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# THE JOURNAL

OF THE

*American Medical Association*

JAN 31 1941

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VOLUME 116, No. 5

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535 North Dearborn Street, Chicago, Ill.

FEBRUARY 1, 1941

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## SUBJECT INDEX TO THIS ISSUE

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*THE JOURNAL of the American Medical Association is published weekly by the American Medical Association 535 North Dearborn Street, Chicago, Ill. Subscription price, $8.00 a year. 25c a copy. Canadian $9.50 Foreign $12.00. Entered as second class matter June 25, 1885, at the Postoffice at Chicago, Ill., under Act of March 3, 1879.*

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# The Journal of the American Medical Association

**Published Under the Auspices of the Board of Trustees**

VOL. 116, No. 5 — COPYRIGHT, 1941, BY AMERICAN MEDICAL ASSOCIATION CHICAGO, ILLINOIS — FEBRUARY 1, 1941


## COMBINED ARTIFICIAL FEVER-CHEMOTHERAPY

### IN GONOCOCCIC INFECTIONS RESISTANT TO CHEMOTHERAPY


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DONALD L. ROSE, M.D.
AND
WALTER M. SIMPSON, M.D.
DAYTON, OHIO


The widespread acceptance of sulfanilamide and other sulfanilyl compounds as effective agents in the treatment of gonococcic infections has modified the value of all preexisting types of therapy. The rapidity with which many cases yield to intelligent and controlled administration of these drugs has obviated the necessity for the use of accessory therapeutic agents in such cases. The brilliance of such results has been dimmed somewhat by the development of several circumstances which will prevent the ultimate eradication of the disease: the asymptomatic carrier,[1] the development of chemotherapy-fast strains of the gonococcus[2] and the occurrence of relapse after apparent cure.[3] Even in instances in which the patient has received what was thought to be adequate treatment, sulfanilamide may fail completely to eradicate the infection. Indeed, in a survey by Dees and Young[4] of 2,727 well analyzed cases collected from the literature only 1,848 (68 per cent) could be classified as immediate cures and an additional 4 per cent as delayed cures. This observation does not imply that sulfanilamide is of limited value in the treatment of gonorrhea; rather, it indicates that even with ideal treatment conditions there will be a considerable proportion of such patients who are not cured by chemicals available at the present time.

Many investigators[5] have demonstrated the value of artificial fever in the treatment of gonorrhea during the presulfanilamide era. Relatively few publications have appeared concerning the effectiveness of artificial fever therapy since the introduction of modern chemotherapy.[6] A few recent publications have dealt with the action of artificial fever in cases of gonorrhea refractory to chemotherapy.[7]

It is our purpose in this paper to point out the value of artificial fever therapy, either alone or combined with chemotherapy, in a series of patients with gonorrhea known to be resistant to sulfanilamide or sulfapyridine.

### EVOLUTION OF FEVER DOSAGE

Treatment of gonococcic infections with artificial fever began in the Kettering Institute for Medical Research in 1932.[8] The first patient so treated was referred for fever therapy because of refractory latent syphilis; he also manifested concurrent clinical and bacteriologic evidence of active gonococcic urethritis and arthritis. During the course of treatment for syphilis, which consisted of five hour sessions at 105-106 F. given once weekly, the arthritis improved immediately and the signs of urethritis gradually disappeared. Succeeding patients treated primarily for gonococcic arthritis received the same fever dosage.[9]

With the observation of Anderson, Arnold, Trautman and Faget[10] in 1934 that semiweekly treatments hastened the disappearance of the urethritis, interest shifted from the treatment of gonococcic arthritis per se to include the eradication of the coexistent genital infec-


From the Kettering Institute for Medical Research, Miami Valley Hospital.


1. Pelouze, P. S.: Gonorrhea in the Male and Female, Philadelphia, W. B. Saunders Company, 1939, pp. 159-169.

2. Westphal, L.; Charles, R. L., and Carpenter, C. M.: The Development of Sulfapyridine-Fast Strains of the Gonococcus, J. Bact. **39:** 47 (Jan.) 1940. Boak, Ruth A.; Charles, R. L., and Carpenter, C. M.: Tolerance of the Gonococcus in Vitro for Increasing Concentrations of Sulfanilamide, Tr. Am. Neisserian M. Soc., 1939, p. 118. Herrold, R. D., and Palmer, E.: The Influence of Sulfanilamide on Gonococci and Gonococcal Infections, Am. J. Syph., Gonor. & Ven. Dis. **22:** 705 (Nov.) 1938.

3. Cokkinis, A. J., and McElligott, G. L. M.: Relapses After Sulfonamide Cure of Gonorrhea, Brit. M. J. **2:** 1080 (Dec. 2) 1939. Cokkinis, A. J.: Discussion of Sulfonamide Therapy in Gonorrhea, Brit. J. Ven Dis. **15:** 117 (April) 1939.

4. Dees, J. E., and Young, H. H.: Present Status of Sulfanilamide Therapy in Gonorrhea, Ven. Dis. Inform. **20:** 33 (Feb.) 1939.

5. These include:
Bierman, W., and Levenson, C.: The Treatment of Gonorrheal Arthritis by Means of Systemic and Additional Focal Heating, Am. J. M. Sc. **191:** 55 (Jan.) 1936. *(Continued in next column)*

5 (continued).
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Owens, C. A.: The Value of Fever Therapy for Gonorrhea, ibid. **107:** 1942 (Dec. 12) 1936.
Humiston, H. W.: Heat and Fever in Treatment of Gonococcus Infections, Am. J. Syph., Gonor. & Ven. Dis. **21:** 554 (Sept.) 1937.
Warren, S. L.; Scott, W. W., and Carpenter, C. M.: Artificially Induced Fever for the Treatment of Gonococcic Infections in the Male, J. A. M. A. **109:** 1430 (Oct. 30) 1937.
Desjardins, A. U.; Popp, W. C., and Stuhler, L. G.: Fever Therapy for Gonococcic Infections, M. Clin. North America **21:** 885 (May) 1937.
Parsons, E. H.; Bowman, P. N., and Plummer, D. E.: Artificial Fever Therapy of Gonorrhea in the Male, J. A. M. A. **109:** 18 (July 3) 1937.
Schnabel, T. C., and Fetter, F.: Fever Therapy in Gonococcal Infections, with Especial Reference to Gonococcal Arthritis, Am. J. Syph., Gonor. & Ven. Dis. **22:** 39 (Jan.) 1938.
Kendell, Webb and Simpson.[9]

6. Krusen, F. H.: Summary of Results of Fever Therapy for Gonorrhea with Follow-up Reports, Proc. Staff Meet., Mayo Clin. **13:** 297 (May 11) 1938. Ballenger, E. G.; Elder, O. F.; McDonald, H. P., and Coleman, R. C., Jr.: Sulfanilamide: I. General Discussion of the Drug; II. Sulfanilamide with the Sealing Treatment of Gonorrhea; III. Sulfanilamide in Combination with Artificial Fever, South. Surgeon **7:** 204 (June) 1938; Sulfanilamide and Thermotherapy, J. A. M. A. **109:** 1037 (Sept. 25) 1937; Artificial Fever in Combination with Sulfanilamide, Urol. & Cutan. Rev. **43:** 441 (July) 1939. Belt and Folkenberg.[35]

7. Elkins and Krusen.[33] Owens, Wright and Lewis.[34]

8. Simpson, W. M.: Artificial Fever Therapy of Syphilis and Gonococcic Infections, Brit. J. Ven. Dis. **12:** 133 (July) 1936. Kendell, Webb and Simpson.[9]

9. Kendell, H. W.; Webb, W. W., and Simpson, W. M.: Artificial Fever Therapy of Gonorrheal Arthritis, Am. J. Surg. **24:** 428 (Sept.) 1935.

10. Anderson, T. B. H.; Arnold, R. C.; Trautman, J. A., and Faget, G. H., in Abstracts of Papers and Discussions, Fifth Annual Fever Conference, Dayton, Ohio, 1935, p. 33.

tion. Attention thus became concentrated on shortening the treatment interval in order to hasten recovery. This plan was quickly adopted by other workers. Desjardins [11] in 1935 reported on the fever treatment of 56 patients giving various manifestations of gonococcic infection with semiweekly five hour sessions at 105-106 F.; after an average of five such sessions, cure was effected. Other workers [5] reported essentially similar results.

Not until the important researches of Carpenter, Boak, Mucci and Warren [12] on the thermolability of different strains of gonococci were the foundations laid for the accurate dosage of fever in the treatment of this infection. Unfortunately, the determination of the thermal death time for a given strain of gonococcus and the subsequent regulation of fever dosage according to the thermal death time of each strain had many barriers in the way of its practical application. Such a procedure is not adaptable to routine performance in the average fever therapy clinic.

*Summary of Results*

| Type of Treatment | Number of Cases | Cure Following Single Session | Average No. of Treatments to Effect Cure | Duration of Disease: Under 3 Mos. Male | Under 3 Mos. Female | Over 3 Mos. Male | Over 3 Mos. Female |
|---|---|---|---|---|---|---|---|
| 8 hrs. 106.6 F. fever | 9 | 9.9% | 2.4 | 3 | 2 | 3 | 1 |
| 10 hrs. 106.6 F. fever | 11 | 63.6% | 1.45 | 4 | 1 | 6 | .. |
| 10 hrs. 106.6 F. fever and 10 days intensive sulfanilamide | 5 | 60.0% | 1.8 | 4 | .. | 1 | .. |
| 10 hrs. 106.6 F. fever and oral sulfanilamide during 18 hrs. before fever | 20 | 100.0% | 1.0 | 7 | 1 | 10 | 1 |
| 10 hrs. 106.6 F. fever and intravenous sulfanilamide immediately before fever treatment | 16 | 81.9% | 1.2 | 4 | 3 | 5 | 4 |
| 10 hrs. 106.6 F. fever and Promin during fever treatment | 11 | 63.6% | 1.3 | 4 | 2 | 5 | .. |
| 10 hrs. 106.6 F. fever and Promin during 18 hrs. before fever | 11 | 100.0% | 1.0 | 4 | 2 | 3 | 2 |
| Total | 83 | ..... | ... | 30 | 11 | 33 | 8 |

Nevertheless, these researches provided the impetus toward the administration of fever in longer sessions, even if the dosage of fever at one session did not approximate the thermal death time of the organism.

At that time the inadequate apparatus and the fragmentary knowledge of the physiology of fever did not permit the use of sustained fever at high levels for long periods. Although long sessions of fever at 106-107 F. were given in this earlier period, they were usually looked on as technical feats and were certainly not to be recommended for the routine treatment of gonorrhea. For this reason the practice of giving multiple short treatments at 105-106 F. was retained.

With improvements in design of the air conditioned cabinet, better insulation, the use of thermostat controls and electrical indicating or recording rectal thermometers, it was found that longer sessions of fever could be tolerated without difficulty, if administered by skilled workers. These factors, combined with a recognition of the necessity for compensating for sodium chloride and fluid loss, cognizance of the dangers inherent in certain types of sedatives and the ability to detect warning signals early, have measurably increased both the safety and the comfort requisites for the satisfactory and practicable administration of artificial fever.

Since it had been observed that longer sessions of fever reduced the total number of treatments required, Krusen [13] in 1937 began using ten hour sessions at 106-107 F. instead of the then standard five hour to eight hour treatments at 105-106 F. By this means he was able to reduce the number of treatments from an average of five to one and one tenth.

At the present time the technic of administering artificial fever has progressed to the point at which patients may now receive a ten hour session at 106.6 F. with far more safety and comfort than was possible with shorter sessions at lower temperature levels in former years. In skilled hands, treatments of this type may be prescribed with a frequency which approaches routine.

### SELECTION OF PATIENTS FOR FEVER TREATMENT

(*a*) *Previous Chemotherapy.*—An earnest attempt has been made to have all the patients included in this report completely comparable in one respect, namely resistance to chemotherapy. Earlier patients had received only sulfanilamide, since sulfapyridine was not at that time generally available. Those subsequently treated had received either sulfanilamide or sulfapyridine or both. A few had received relatively small amounts of chemotherapy because of the development of one or more of the following untoward reactions: blurred vision, extreme nausea and vomiting, acute hemolytic anemia, fever, hepatitis, jaundice and dermatitis.

(*b*) *Duration of the Disease.*—Fever therapy has not been limited to any particular manifestation or stage of the disease. Since we dealt with drug-resistant patients, no one treated had had the disease for less than two weeks. No attempt has been made to classify the condition as acute, subacute or chronic on the basis of duration of symptoms. The patients are arbitrarily divided into two groups: those in whom the duration of the disease was more than three months or less than three months. The table reveals that approximately one half of the patients fall into each group.

(*c*) *Complications of the Disease.*—No patient was treated for uncomplicated anterior urethritis. All varieties of complications were treated, varying from the relatively minor one of prostatitis to severe pan-pelvic inflammation. Seven patients were completely asymptomatic, falling into the class of so-called carriers; each of these had received previously extensive chemotherapy.

(*d*) *Sex.*—Patients of either sex received treatment without selection. The table reveals a sex distribution ratio of roughly three males to one female.

(*e*) *Age.*—Age alone was no bar to treatment, provided the diagnostic survey revealed no contraindications. The age limits varied from 16 to 56 years, with a mean age of 27 years.

(*f*) *Contacts.*—Whenever possible, all suspected "contacts" were examined bacteriologically and clinically. In addition to those found to be obviously infected, seven completely asymptomatic persons yielded positive cultures from secretions of the genital tract.

11. Desjardins, A. U.; Stuhler, L. G., and Popp, W. C.: Fever Therapy for Gonococcic Infections, J. A. M. A. **104**: 873 (March 16) 1935.

12. Carpenter, C. M.; Boak, Ruth A.; Mucci, L. A., and Warren, S. L.: Studies on the Physiologic Effects of Fever Temperatures, J. Lab. & Clin. Med. **18**: 981 (July) 1933.

13. Krusen, F. H.; Randall, L. M., and Stuhler, L. G.: Fever Therapy plus Additional Local Heating in the Treatment of Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **22**: 185 (March) 1938.

### CARE OF THE PATIENT DURING HOSPITALIZATION

The technic by which the earlier treatments were carried out has been described in previous publications.[14] The changes which have accrued in our methods within the past two years have been described in detail elsewhere.[15]

All patients are hospitalized. Eligiblity for fever therapy is determined after a thorough diagnostic survey, which includes a careful history, a complete physical examination and all indicated laboratory procedures. The apparatus employed was the hypertherm.

Most of the patients received a short preliminary "pilot" treatment, the purposes of which were to test the patient's physiologic responses to fever and to allay apprehension and to accustom him to lying in a warm, humid environment. The pilot treatment was given at a lower rectal temperature, usually 105 F., and was of three hours' duration. The last few patients included in this report received no preliminary pilot treatment. Their reactions, during and subsequent to the ten hour treatment, differed in no significant degree from those who also received the pilot treatment.

For the long treatment session the rectal temperature was elevated to 106.6 F. and was maintained at this level for either eight or ten hours. Throughout the treatment, except for brief rest periods, pure oxygen was supplied by means of the Boothby-Lovelace-Bulbulian[16] nasal mask in quantities sufficient to maintain an alveolar oxygen concentration of 60 per cent or more. At intervals of three hours the patient received 50 cc. of a 50 per cent solution of dextrose intravenously. No other fluids were given intravenously. He was encouraged to take by mouth 300 to 400 cc. an hour of iced 0.6 per cent solution of sodium chloride in tap water. The sedative used was pantopon[17] by hypodermic injection in doses of 1/6 to 1/3 grain (0.01 to 0.02 Gm.). Many patients required no sedative and few needed more than one such injection. The pulse rate seldom exceeded 130 beats per minute during the maintenance period and averaged 120 to 130 beats per minute. The cabinet doors were not opened except for intravenous injections, blood pressure recordings or checking the resistance wound rectal thermometer with a certified mercury thermometer. The constant inspection of the skin, which in former years was necessary to prevent burns, is unnecessary, since, with the low dry bulb temperatures now used, burns, are unknown and even erythema of a mild degree is not seen.

During each of the succeeding three days, the genital secretions were collected for smears and cultures. Cultures were made on two types of mediums: McLeod's[18] medium and the plasma-agar medium developed by us.[19] During the past year only the latter medium was used. Culture mediums were incubated according to Thompson's[20] simplified technic for production of increased carbon dioxide tension. At the end of twenty-four hours the cultures were inspected and organisms from oxydase-positive[21] colonies were stained by Gram's method. If deemed advisable, a pure strain of the organism was isolated and its identity established by fermentation tests. An organism was accepted as being the gonococcus if it was a gram-negative diplococcus which grew poorly if at all on plain agar and which fermented only dextrose.

If the results of the bacteriologic examinations were negative for gonococci, the patient was dismissed and was then followed as an outpatient for at least three months.

### CRITERIA OF CURE

The term "cure" is employed in the bacteriologic as well as the clinical sense. The criteria of clinical cure in the male included complete resolution of the presenting clinical symptoms, absence of pus and shreds of mucus in the urine, restoration of the prostatic fluid toward normal, and failure of the usual "provocative" tests (massage of the periurethral glands over a urethral sound, and repeated prostatic massage) to influence the clinical status. It is our observation that little reliance can be placed on the clinical status alone in determining cure. Seven of the patients treated were asymptomatic from the outset, the diagnosis having been established solely on bacteriologic findings. Since the cultural methods employed have been so dependably accurate, we have relied chiefly on the bacteriologic findings in determining cure. Periodic cultural reexaminations of the genital secretions were carried out for a period of at least three months. In the female, pelvic examinations were done on the first postmenstrual day of each of the three menstrual periods following the treatment.

No patient was included in this series who had not been under observation for at least three months. A few of the patients were followed carefully for from two to two and one-half years.

### EXPERIMENTAL DATA

This series comprises a total of 83 patients who presented complications of gonorrhea and who were either presumably resistant or intolerant to sulfanilamide or to sulfapyridine or to both drugs.

The different groups of patients were divided as follows:

1. Those receiving fever alone:

(*a*) Eight hour sessions at 106.6 F.[22]

(*b*) Ten hour sessions at 106.6 F.

2. Those receiving fever in combination with chemotherapy:

(*a*) Ten hour sessions at 106.6 F. with oral sulfanilamide during eighteen hours before fever.

(*b*) Ten hour sessions at 106.6 F. with intravenous sulfanilamide immediately before fever.

14. Simpson, W. M.: Artificial Fever Therapy of Syphilis and Gonococcic Infections, Brit. J. Ven. Dis. **12:** 133 (July) 1936; Behandlung der Syphilis und der Gonorrhea mit künstlich erzeugtem Fieber, Wien. klin. Wchnschr. **49:** 779 (June 19) 1936. Simpson, W. M., and Kendell, H. W.: Artificial Fever Therapy, Colorado Med. **34:** 782 (Nov.) 1937. Rueth, M. L.: Nursing Technic in Artificial Fever Therapy, Ohio Nurses Rev. **14:** 10 (Jan.) 1939.

15. Kendell, H. W.; Rose, D. L., and Simpson, W. M.: Fever Therapy Technic in Syphilis and Gonococcic Infections, Arch. Phys. Therapy **20:** 614 (Oct.) 1939.

16. Boothby, W. M.: Oxygen Administration: The Value of High Concentration of Oxygen for Therapy, Proc. Staff Meet., Mayo Clin. **13:** 641 (Oct. 12) 1938. Lovelace, W. R.: Oxygen for Therapy and Aviation: An Apparatus for the Administration of Oxygen or Oxygen and Helium by Inhalation, ibid. **13:** 646 (Oct. 12) 1938. Bulbulian, A. H.: Design and Construction of the Masks for the Oxygen Inhalation Apparatus, ibid. **13:** 654 (Oct. 12) 1938.

17. A preparation of the hydrochlorides of the alkaloids of opium, principally morphine.

18. McLeod, J. W.; Coates, J. C.; Happold, J. C.; Priestley, D. P., and Wheatley, B.: Cultivation of the Gonococcus as a Method in the Diagnosis of Gonorrhea, with Special Reference to the Oxydase Reaction and to the Value of Air Reinforced in Its Carbon Dioxide Content, J. Path. & Bact. **39:** 221 (July) 1934.

19. Rose, D. L.; Kendell, H. W., and Simpson, W. M.: A Plasma-Agar Medium for Cultivation of the Gonococcus, Am. J. Clin. Path. **10:** 59 (May) 1940.

20. Thompson, L.: A Simple Method of Supplying Carbon Dioxide in Jars for Bacteriological Cultures, Am. J. Clin. Path. **5:** 313 (July) 1935.

21. Gordon, J., and McLeod, J. W.: The Practical Application of the Direct Oxydase Reaction in Bacteriology, J. Path. & Bact. **31:** 185 (April) 1928.

22. All records of temperature refer only to rectal temperature, as determined by continuously operating electrical indicating thermometers.

(*c*) Ten hour sessions at 106.6 F. with concomitant Promin.

(*d*) Ten hour sessions at 106.6 F. with Promin during eighteen hours before fever.

1. (*a*) *Those Receiving Eight Hour Sessions of Fever Alone.*—This group comprises 9 patients. As shown in the table, only 1 patient in this group was bacteriologically negative following a single eight hour session at 106.6 F. The number of such treatments required to effect cure in this group averaged two and four tenths. Although considerably better than the average of four and eight tenths five hour sessions during the presulfanilamide era,[9] this plan of treatment did not appear to possess the merit of the longer ten hour sessions and was abandoned in favor of the latter.

(*b*) *Those Receiving Ten Hour Sessions of Fever Alone.*—The treatment of patients in this group followed the same plan as that described previously with the exception that ten hours instead of eight hours of fever at 106.6 F. were given. The results, as shown in the table, indicate that 10 of the 16 patients (62.5 per cent) recovered from the infection following a single ten hour session at 106.6 F. The average number of such treatments required was one and fifty-six one hundredths. Even though these patients may have received an adequate total dose of sulfanilamide prior to hospitalization, it could be argued that they were not necessarily sulfanilamide resistant, since either insufficient individual doses or failure to give the drug during the night would militate against an effective sustained blood (and tissue) concentration. For this reason an unselected group of 5 consecutive patients, all of whom were believed to be resistant to sulfanilamide, were hospitalized. Sulfanilamide was then given under strictly controlled conditions in the dosages recommended by Long and Bliss.[23] A sufficient amount of this drug was given to maintain the blood sulfanilamide level between 10 and 12 mg. per hundred cubic centimeters for a period of ten days. The dosage employed varied but averaged 20 grains (1.3 Gm.) every four hours, or a total of 120 grains (8 Gm.) daily. At the end of this period the 5 patients still presented active clinical symptoms of gonorrhea, and the genital secretions were bacteriologically positive for Neisseria gonorrhoeae. These patients were then given ten hour sessions of fever at 106.6 F. and are included in the total of the 16 patients comprising this group. It is worthy of mention that, despite the careful maintenance of the blood sulfanilamide concentration at a high level for an extended period of time, as a group these patients were no more susceptible to fever than those who had not received such intensive, controlled medication; one and eight-tenths ten hour sessions were required to effect cure in this group as compared with one and forty-five one hundredths similar sessions for others in the ten hour group.

2. (*a*) *Those Receiving Ten Hours of Fever Combined with Oral Sulfanilamide During Eighteen Hours Before Fever.*—Since there seemed to be no virtue in an intensive ten day course of sulfanilamide prior to fever, this procedure was abandoned. Wengatz, Boak and Carpenter [24] and Warren have shown that in the presence of a concentration of 1 : 10,000 of sulfanilamide the thermal death time of a given strain of gonococcus was lowered approximately 50 per cent. An attempt was made in this group of patients to apply this principle by the application of artificial fever at a time when a 1 : 10,000 concentration (10 mg. per hundred cubic centimeters) of sulfanilamide was present in the body.

This group consists of 20 unselected patients of the same type as that comprising the preceding series. The comparison of this group with those groups receiving fever alone is shown in the table.

All received the same type of treatment as that which has been described previously with one exception: Beginning at 2 p. m. on the day following the pilot treatment, sulfanilamide was given by mouth. The initial dose for persons weighing over 150 pounds (68 Kg.) was 80 grains (5.2 Gm.); for persons weighing less than 150 pounds, 60 grains (4 Gm.) was given. Thereafter, at intervals of four hours, maintenance doses, each of 20 grains (1.3 Gm.), were given. Thus, a total of 140 (9 Gm.) or 160 (10 Gm.) grains of the drug was given over a period of eighteen hours in five doses. The blood sulfanilamide concentration, as determined by the method of Marshall,[25] or, more recently, by the method of Bratton and Marshall [26] as adapted to the Sheard-Sanford "photelometer," [27] averaged 12 mg. per hundred cubic centimeters at the time the patient was placed in the cabinet. Starting at 7 o'clock the following morning, eighteen hours after the administration of sulfanilamide was begun, the patients received a ten hour session of fever at 106.6 F. No additional sulfanilamide was given.

The results in this group were much more encouraging. No patient demonstrated clinical or bacteriologic evidence of gonococcic infection after the single ten hour session of fever when the blood sulfanilamide concentration had been elevated to from 10 to 12 mg. per hundred cubic centimeters at the commencement of the fever session. The sulfanilamide concentration of the blood at the conclusion of the ten hour fever treatment averaged 8 mg. per hundred cubic centimeters. It may be assumed, therefore, that a 1 : 10,000 concentration of sulfanilamide was present in the tissues for at least the greater part of the ten hour session and would seem to lend some support to the conclusions of Wengatz and his co-workers [24] as far as it is possible to make an analogy between in vitro and in vivo experiments.

From the practical standpoint, however, we were not satisfied with this program. The amount of sulfanilamide given during the eighteen hours preceding the fever treatment appeared to have a definite influence on the patients' reactions during the treatment. The actual amount of fever administered was the same as that given to those patients who had received no sulfanilamide. Hence any changes exhibited by the patient could reasonably be attributed only to the drug.

Since it was necessary to administer the drug at frequent and regular intervals during the day and night, it was customary for patients to report to the fever therapy department with the complaint that they had had little or no sleep during the night. Consequently the patient was relatively exhausted before the fever treatment was started. This was undesirable, since it had been found that those patients who were well rested when they came to the long treatment

23. Long, P. H., and Bliss, Eleanor A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, Macmillan Company, 1939.

24. Wengatz, H. F.; Boak, Ruth A., and Carpenter, C. M.: The Bactericidal Effect of Sulfanilamide on the Gonococcus in Vitro, J. Bact. **35**: 36 (Jan.) 1938.

25. Marshall, E. K.: Determination of Sulfanilamide in Blood and Urine, J. Biol. Chem. **122**: 263 (Dec.) 1937.

26. Bratton, A. C., and Marshall, E. K.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**: 537 (June) 1939.

27. Sanford, A. H.; Sheard, C., and Osterberg, A. E.: The Photelometer and Its Use in the Clinical Laboratory, Am. J. Clin. Path. **3**: 405 (Nov.) 1933.

tolerated the treatment much more readily than those who were fatigued. The unfortunate tendency of sulfanilamide to produce nausea and occasional vomiting was evident in all of these patients. Thus, in addition to being more or less exhausted the patient was also nauseated, and often vomiting, before the fever session was begun. Almost without exception they also exhibited the bluish discoloration of the skin and mucous membranes characteristic of persons receiving sulfanilamide. This circumstance made it difficult to judge the state of oxygenation of the blood during the subsequent fever period by the appearance of the skin and mucous membranes. Finally, the known tendency of sulfanilamide also to produce dizziness, headache, mild mental confusion and delirium was definitely exaggerated at a temperature of 106.6 F.

Therefore, without denying that such a combined form of chemical and fever treatment was highly effective therapeutically, a method was sought to attain the same result without the presence of these annoying side complications.

(*b*) *Those Receiving Sulfanilamide Administered Intravenously Immediately Before Fever.*—Sixteen patients are included in this group, the results of whose treatment are shown in the table. The pretreatment medication schedule of these patients was as follows: The patient was permitted to rest the day and night preceding the long treatment. One hour before the ten hour fever session, sulfanilamide was given intravenously in the form of an 0.8 per cent solution (in physiologic solution of sodium chloride), the dosage being calculated on the basis of ¾ grain (0.05 Gm.) per pound of body weight. The solution was prepared immediately prior to administration. The actual amount of sulfanilamide thus given was somewhat less than that which is given orally to patients of group 2 a. Such dosage was sufficient to produce blood sulfanilamide concentrations of 10 mg. or more per hundred cubic centimeters of blood for the duration of the fever treatment. The administration of the drug one hour before the fever treatment was thought to allow sufficient time for its complete distribution throughout the fluids of the body.[28]

From the practical standpoint, such a program appeared to remove the difficulties inherent in the oral method of administration of the drug. Toxic reactions were strikingly diminished and in many patients were completely absent. Since the amount of fever administered to the two groups was exactly the same, the type of patient was the same and the blood sulfanilamide concentrations were practically identical in the two groups, we anticipated that the therapeutic results would be comparable. This did not prove to be the case.

Of these 16 patients, only 13 were cured by the single ten hour fever session combined with sulfanilamide given intravenously. Even with due regard to the small number of patients included in either group, the differences seemed to be statistically significant. We were therefore forced to the conclusion that the mere presence of sulfanilamide in a 1:10,000 concentration at the time the fever was given does not wholly explain its therapeutic action and hence that the in vitro experiments of Wengatz and his associates could not be translated directly to in vivo conditions.

(*c*) *Those Receiving Fever Combined with Promin During the Treatment.*—Promin,[29] the sodium salt of p,p′-diaminodiphenylsulfone-N,N′-di (dextrose sulfonate), differs from other similar compounds in its high degree of solubility. It is prepared as a stable 40 per cent aqueous solution which is suitable for parenteral injection. Because of its extreme solubility, it is possible to administer relatively large quantities of the drug in a minimum amount of solvent. For example, 5 Gm. of Promin may be administered in a total solution volume of 12.5 cc. Furthermore, because of such ready solubility in aqueous fluids, it was thought that diffusion in the body fluids should be more rapid and complete than is the case with sulfanilamide.

Its therapeutic efficacy, particularly in the treatment of gonococcic infections, was largely undetermined. Therefore a series of patients were subjected to the same type of experimental program as that described under group 2 b with the exception that, instead of sulfanilamide being administered immediately prior to the treatment, 5 Gm. of Promin was injected intragluteally when the fever treatment was started and every three hours during the treatment. Thus a total of 20 Gm. of the drug was given during the ten hour session of fever. Blood Promin concentrations, determined by a suitable adaptation of the method of Bratton and Marshall,[26] averaged from 10 to 15 mg. per hundred cubic centimeters for the duration of the treatment. Excretion of the drug following the treatment appeared to be very rapid, since only traces could be found in the blood from twelve to sixteen hours later.

With the exception of a moderate degree of irritation at the site of injection, which disappeared within twenty-four hours, this compound was uniformly well tolerated. The toxic reactions common to sulfanilamide were not observed. In a minority of the patients, toward the end of the fever session a mild degree of "cyanosis" of the skin and mucous membranes was evident. There was no dizziness, confusion, headache, gastrointestinal upset or other sign of toxicity of the type commonly observed following the oral administration of sulfanilamide.

Of the group of 11 patients with refractory gonococcic infection subjected to this program, only 7 were cured following a single fever session of ten hours at 106.6 F. Therefore it was felt that there were no advantages in the concurrent use of Promin and fever therapy, as administered to these patients, over fever therapy alone.

(*d*) *Those Receiving Ten Hours of Fever Combined with Promin During Eighteen Hours Before Fever.*—Since Promin is known to be an effective compound [30] and because we had observed an apparent potentiation of the action of sulfanilamide when administered during a period of eighteen hours prior to fever, a final experiment was designed to test the hypothesis that Promin likewise might be more effective when administered for a definite period before the fever session.

The schedule of Promin administration in this group was as follows: Beginning at 2 o'clock on the afternoon preceding the long treatment session and at intervals of four hours thereafter, the patient received 5 Gm. injections of Promin intramuscularly. Thus a total of 25 Gm. of the compound was given during the eighteeen hour period prior to the fever treatment. None was given during the fever session.

28. Painter, E. E.: The Application of Spectrographic Methods to the Determination of Total Body Water with Sulfanilamide, in Proceedings of the Sixth Summer Conference on Spectroscopy and Its Application, Massachusetts Institute of Technology, 1939, p. 125.

29. Promin was supplied by Dr. E. A. Sharp, director of clinical investigation, Parke, Davis & Co., for investigative purposes.

30. Greey, P. H.; MacLaren, D. B., and Lucas, C. C.: Comparative Chemotherapy in Experimental Pneumococcal Infections, Canad. M. A. J. **40**: 319 (April) 1939.

The blood Promin concentrations at the beginning of the treatment were considerably higher than those noted in the preceding group of patients, although excretion of the drug appeared to be more rapid. The initial concentration of the drug in the blood averaged 23 mg. per hundred cubic centimeters; at the conclusion of the treatment it averaged 7 mg. per hundred cubic centimeters.

Signs of toxicity were minimal. A noticeable degree of the bluish discoloration of the skin and mucous membranes was present in all of these patients, comparable to that produced by sulfanilamide. In the majority of cases a definite methemoglobin band could be detected on spectroscopic examination of the blood. Despite the necessity for awakening the patient during the night to administer the drug, the complaint of insomnia was practically absent. Headache, nausea, dizziness, confusion and delirium were not encountered. Of special interest was the almost complete absence of the post-fever depression customarily seen the day following the long treatment session in those persons receiving sulfanilamide.

The therapeutic efficacy of this type of treatment, as measured by cure following the single session of ten hours of fever at 106.6 F., compares favorably with that noted in group 2 a. All of the 11 patients in this group were cured following the single long treatment. If this high degree of therapeutic efficacy can be maintained, it would appear that this is the treatment of choice.

## COMMENT

It is felt that these observations provide at least a partial answer to a number of pertinent questions which have been raised regarding the treatment of gonococcic infections. One of the first queries concerned the possibility that resistance to chemotherapy might also be paralleled by resistance to other forms of therapy, including artificial fever. It has been reported [31] that, in those cases in which sulfanilamide has failed to cure, fever therapy has been equally ineffective. Our experiences indicate that there is no correlation between variations in chemolability and in thermolability. The amount of fever necessary to effect cure in those patients who received fever therapy alone included in Groups 1 a and b closely approximates that reported [13] in the pre-sulfanilamide era.

Artificial fever combined with chemotherapy has been reported [6] to be highly effective in the treatment of gonococcic infections. The occurrence of drug fever during the course of sulfanilamide medication has also been noted [32] to cause a definite shortening of the course of the disease.

The role of artificial fever combined with chemotherapy in those cases resistant to the drug alone has not been well defined. Elkins and Krusen [33] have reported that in forty-three cases of sulfanilamide-resistant gonorrhea an average of one and two-tenths ten hour sessions at 106.6 F. has effected cure with sulfanilamide given in daily dosages of 80 grains (5.2 Gm.) for two days preceding the fever treatment. Owens, Wright and Lewis [34] have reported that 4 patients with sulfanilamide-resistant gonorrhea were cured by a single fever treatment when they were given "large doses of sulfanilamide for three or four days and then, when they had attained the usual saturation with the drug, giving them the ten hour fever treatment." Belt and Folkenberg,[35] in a series of 49 patients with refractory gonococcic infections, were able to effect cure in 86 per cent by the combination of artificial fever and chemotherapy.

The interesting variation in therapeutic effectiveness in the two modes of administration of sulfanilamide presented in this report raises several important questions. Is the difference in effectiveness related to blood concentration alone? In general, those patients receiving sulfanilamide intravenously attained somewhat higher concentrations than those receiving the drug orally. Indeed, in several patients in group 2 a the blood level was only approximately one-half the average for the group as a whole; yet these patients responded no differently than did those possessing higher blood concentrations. In the literature, furthermore, there is no general agreement as to what constitutes the maximum effective blood concentration; from 1 to 2 mg. per hundred cubic centimeters has been reported [36] to be as effective experimentally as 10 mg. per hundred cubic centimeters.[23] Perhaps this discrepancy may be explained on the basis of the observation [37] that there is no correlation between resistance of a given strain of gonococcus to sulfanilamide in vivo and its behavior in a test tube. If this observation is essentially correct, it might also indicate that the therapeutic difference between groups 2 a and 2 b may be due neither to a lowering of the thermal death time, as the work of Wengatz would suggest, nor to a thermal potentiation of the bactericidal action of sulfanilamide, as the work of White [38] would imply.

Is the difference one of relative rather than actual resistance to sulfanilamide? A growing body of evidence has accumulated which indicates that it is possible to produce drug-fast strains of gonococci in vivo [2] during the course of chemotherapy, a type of resistance which appears to be "permanent" (i. e., it persists in subcultures). Providing some support to this theory is the small number of patients included in group 1 b, in which a ten day period of intensive sulfanilamide therapy failed to influence the course of the disease either bacteriologically or clinically. In this connection it may also be stated that at no time during this ten day period was there any difficulty in cultivating the gonococcus from the genital secretions, nor did there appear to be any tendency toward the appearance of atypical forms of the organism.

The mere presence of sulfanilamide alone does not completely explain its action, as the results of the treatment of the patients in group 2 b demonstrate. We therefore incline to the opinion that, during the eighteen hour period of administration of the chemotherapeutic agent prior to fever therapy, potentiation of some factor within the body occurs; whether this is in the direction of stimulation of the body's defensive mechanisms or is in the nature of attenuation of the offensive mechanism of the gonococcus is not clear. The available evi-

31. Crenshaw, J. L., and Cook, E. N.: Limitations, Dangers and Failures of Sulfanilamide in Treatment of Urinary Tract Infections, J. Urol. **41**: 64 (Jan.) 1939.

32. Lich, R., and Rowntree, G. R.: Sulfanilamide Therapy in Acute Neisserian Urethritis, Am. J. Syph., Gonor. & Ven. Dis. **23**: 323 (May) 1939.

33. Elkins, E. C., and Krusen, F. H.: Clinical Results of Fever Therapy, Arch. Phys. Therapy **20**: 346 (June) 1939.

34. Owens, C. A.; Wright, W. D., and Lewis, M. D.: The Value of Fever Therapy in Sulfanilamide-Resistant Gonorrhea, J. Urol. **40**: 847 (Dec.) 1938.

35. Belt, A., and Folkenberg, A. W.: Treatment of Gonorrhea by Artificial Fever Alone and in Combination with Sulfanilamide, Arch. Phys. Therapy **21**: 203 (April) 1940.

36. Osgood, E. E., and Brownlee, I. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, J. A. M. A. **110**: 349 (Jan. 29) 1938. Finkelstein, R., and Birkeland, J. M.: Mode of Action of Sulfanilamide and Prontosil, Science **87**: 441 (May 13) 1938.

37. Cohn, A.; Jacoby, A.; Kornblith, B. A., and Wishengrad, M.: A Clinical and Experimental Evaluation of Sulfanilamide in Gonorrhea, Am. J. Syph., Gonor. & Ven. Dis. **23**: 41 (Jan.) 1939.

38. White, H. J.: The Relationship Between Temperature and the Streptococcidal Activity of Sulfanilamide and Sulfapyridine in Vitro, J. Bact. **38**: 549 (Nov.) 1939.

dence concerning the bacteriostatic nature of the action of the drug would seem to support the latter thesis.

Finally, the public health implications of such a highly effective method of treatment should not be overlooked. The ultimate goal in the control of venereal diseases should be methods which will quickly and surely eliminate the infection. With such a therapeutic system as that outlined in the text of this paper, combined with adequate case-finding methods for the purposes of discovering and treating "contacts," the venereal disease control program advocated by the U. S. Public Health Service could be achieved in a much shorter time and with greater assurance of actual cure than by present day methods.

### CONCLUSIONS

1. Eighty-three patients suffering from complications of gonorrhea, resistant or intolerant to chemotherapy, have been treated with artificial fever, either alone or combined with chemotherapy.

2. Of those refractory patients receiving fever therapy alone, only 12.5 per cent were cured following a single eight hour treatment at 106.6 F.; 62.5 per cent were cured following a single ten hour treatment at 106.6 F.

3. When combined with artificial fever, the effectiveness of chemotherapy (sulfanilamide or Promin) is influenced by the time-dosage relationship with respect to the fever treatment; when administered for eighteen hours preceding the fever treatment, the effectiveness is much greater than when administered immediately prior to or during the treatment.

4. A ten day period of intensive sulfanilamide therapy prior to fever therapy is without value in sulfanilamide-resistant patients, provided none of the drug is present in the body fluids at the time of the fever treatment.

5. All of 31 unselected consecutive patients treated with sulfanilamide or Promin for eighteen hours before a single ten hour fever session at a rectal temperature of 106.6 F. were cured.

6. Rigid bacteriologic criteria were employed as the chief basis for the determination of cure.

7. The combination of a single ten hour session of artificial fever therapy combined with the administration of adequate sulfanilamide or Promin for eighteen hours prior to the fever treatment appears to be the procedure of choice in the treatment of chemotherapy-resistant gonococcic infections.

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**Diphtheria and Acute Tonsillitis.**—There is a striking contrast between the onset of an attack of acute tonsillitis and an attack of diphtheria. Tonsillitis begins explosively with a chill, high fever, nausea, vomiting, headache, backache and a fiery red and swollen throat, which renders swallowing an exceedingly painful act. The victim is obviously very ill from the start. . . . Diphtheria, however, does not announce itself in any such dramatic manner. It begins after an incubation period of from one to five days, with a little fretfulness and lassitude. The favorite games and toys no longer interest. The appetite is capricious, but since swallowing is performed without difficulty, and since there is no change in the voice nor complaint of sore throat, the possibility of diphtheria is not suspected by the average parent. The mouth temperature at this stage is only slightly above normal, rarely more than 100 or 101 F., and this serves further to allay suspicion. The diagnosis of diphtheria should not be discarded, however, because the temperature is higher than 101 F.—Holmes, William H.: Bacillary and Rickettsial Infections—Acute and Chronic, New York, Macmillan Company, 1940.

## ANORECTAL OPERATIVE PROCEDURES WITH SPECIAL REFERENCE TO THE AVOIDANCE OF PAIN

### BASED ON A SERIES OF ONE THOUSAND CASES

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A statistical report recently published by a large insurance company gives the incidence of hemorrhoidal disease as one fifteenth of the total population of the United States. If these individual case records were carefully studied it is highly probable that many allied conditions of the anorectum were included in the original survey. In part, at least, this report gives evidence of the frequency of the disease. It is not my purpose in this presentation to discuss the prevention of hemorrhoidal disease although it may be said that much has been accomplished in respect to education of persons, especially the young, as to the value of a regular daily evacuation, a well balanced diet, the avoidance of drastic cathartics and periodic complete examination.

For treatment, conservative measures may be employed with satisfaction, but in the vast majority of anorectal disorders surgical intervention is required. Rectal operations enjoy an unenviable reputation for postoperative pain among both physician and the laity, and unfortunately this reputation is not altogether unfounded. The important question is, why do patients experience such severe pain and what measures can be taken for its prevention or decrease? The abundant nerve supply to the lowermost portion of the intestinal tube (anal canal) and perianal areas, which is derived from the somatic portion of the cerebrospinal nervous system, accounts for its marked sensitivity; therefore, distress of varying intensity incidental to surgical trauma is physiologic. Of utmost importance, however, is the contraction of the voluntary anorectal muscles, especially the external sphincter, which is so frequently associated, giving rise to that which is termed "sphincter spasm." Of course, above the anorectal line (union of rectum with anal canal) the innervation is sympathetic and parasympathetic.

Largely through the efforts of proctologists here and abroad, constant progress has been made toward rendering the postoperative course less painful through the injection of oil-soluble anesthetics. All will agree that their use, while of advantage and to be advocated, is inadequate. Is it not consistent with sound reasoning that the operative factors influencing the degree of pain be considered as well as the relief?

Pain postoperatively, immediate and remote, is due largely to spasmodic contraction of the external sphincter muscle. A careful analysis of each case in several large series revealed that this "sphincter spasm" was due not to one but to many factors, namely unnecessary trauma to the tissues accentuated by inhalation anesthetics; failure to respect the continuity of the anorectal juncture and to preserve adequate anal and adjacent perianal skin; inclusion of the external sphincter muscle, wholly or in part, in the suture or clamp; omission of one of the prolonged aqueous analgesic solutions; the employment of the usual abusive whistles or packs, and improper as well as inadequate after-care. With

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Read before the Section on Gastro-Enterology and Proctology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

this in mind, I recommend the operative procedures on an anatomic basis and according to the pathologic condition present.

During the four year period ending February 1940 operation has been performed on 1,033 patients, which number includes only those procedures commonly asso-

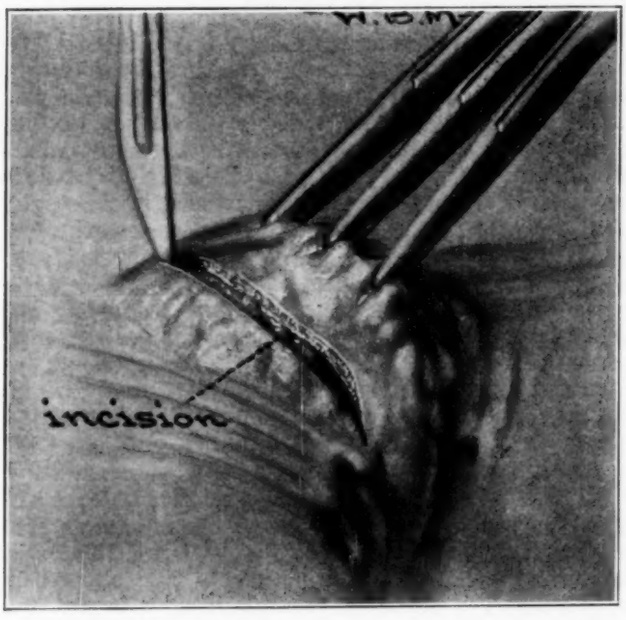


Fig. 1.—Incision in skin high on lateral wall of the hemorrhoid, beginning at the anorectal line.

ciated with pain. While it can be frankly stated that no one group of persons was absolutely free of pain, and even though the problem of absolute relief is far from its solution, the results have been so favorable and encouraging that I take this opportunity of reporting my experience.

For the purpose of brevity and because radical hemorrhoidectomy is rightly to be considered the most painful procedure on the anorectum, only this technic is

TABLE 1.—*Dosage of Analgesic Solution*

| Weight in Pounds | Dose in Mg. | Lumbar Interspace |
|---|---|---|
| 70 - 100 | 40 | 4th |
| 101 - 150 | 50 | 4th |
| 151 - 170 | 60 | 4th |
| 171 - 190 | 70 | 4th |
| 191 - 210 | 80 | 4th |
| 211 - 220 | 90 | 4th |
| 221 - 240 | 100 | 4th |

described. The preoperative sedation and anesthetic, and the postoperative care differ but little with the various surgical procedures. Strict adherence to every detail is essential. The procedure is as follows: The patient is hospitalized the night prior to operation; an enema of physiologic solution of sodium chloride is administered through a small rubber catheter, and pentobarbital sodium, 1½ grains (0.09 Gm.), is given by mouth. The following morning the perineum and lumbosacral regions are closely shaved and prepared. In addition to the usual physical examination, the blood pressure readings are made of both arms and the weight of the patient tabulated. Complete blood cell count, blood chemistry and urinalysis are routine procedures. The second and first hour before operation, pentobarbital sodium in 1½ grain (0.09 Gm.) doses is given by mouth.

*Analgesia.*—Low lumbar (spinal), sacral, caudal, combined or conduction analgesia is employed. In the series of patients previously cited, approximately 90 per cent were given a block low in the lumbar region, the dose of the analgesic solution being determined by the body weight of the patient.

For the purpose of sustaining blood pressure during operation, neosynephrin hydrochloride according to the preoperative pressure with procaine hydrochloride is injected into the fourth lumbar interspace.

*Surgical Technic.*—With the patient in the jack-knife or inverted position, the sphincter muscles are gently massaged and the anorectum is cleansed. The gloves

TABLE 2.—*Dosage of Neosynephrin Hydrochloride*

| Systolic Blood Pressure, Left Arm | Dosage of Neosynephrin Hydrochloride |
|---|---|
| 131 to 140 | 0.1 cc. in 1 cc. 0.5% procaine hydrochloride |
| 121 to 130 | 0.2 cc. in 1 cc 0.5% procaine hydrochloride |
| 111 to 120 | 0.3 cc. in 1 cc. 0.5% procaine hydrochloride |
| 101 to 110 | 0.4 cc. in 1 cc. 0.5% procaine hydrochloride |
| 90 to 100 | 0.5 cc. in 1 cc. 0.5% procaine hydrochloride |

used for the analgesia and gentle divulsion are discarded. The operator dons sterile gown and gloves, and the perianal region is prepared. After appropriate drapes are in place, the hemorrhoidal masses are drawn outside the anus in their respective quadrants by means of curved Rankin hemostats. Additional hemostats are applied to the hemorrhoid to bring into view as much hemorrhoidal tissue as possible without undue tension. Where external hemorrhoids are present, a small elliptic incision is made high on the lateral side of each beginning at a point just distal to the anorectal line and

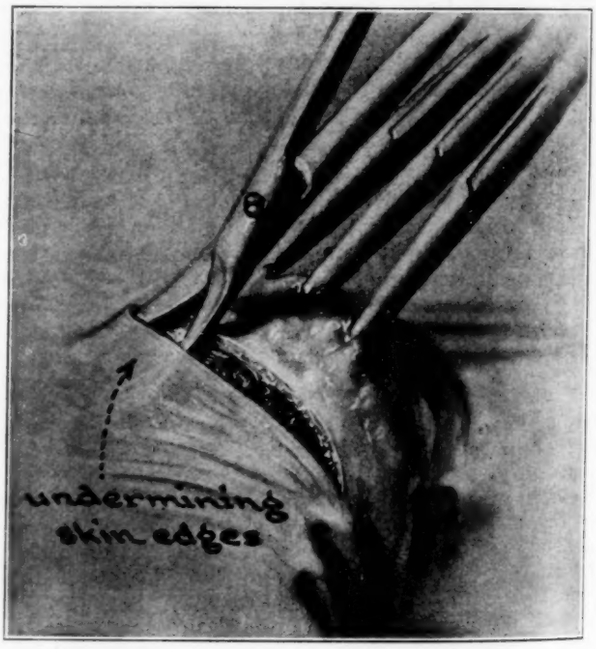


Fig. 2.—By means of small curved scissors the subcutaneous veins are separated for preservation of the skin.

carried to a point one-half inch beyond the tip of the external hemorrhoidal mass. The outer leaf of skin on each side of the hemorrhoid is elevated with fine tissue forceps and separated from the underlying tissue by means of small blunt-tipped curved scissors. The hemorrhoid is elevated, and blunt dissection is begun at the apex where the two incisions are joined. The

adjacent veins, which have been freed on either side, are drawn medially by an assistant, and the operator continues with the blunt dissection on the surface of the external sphincter muscle. When the inner edge of this muscle is encountered, a small right angle retractor is placed so as to draw the muscle gently from the field

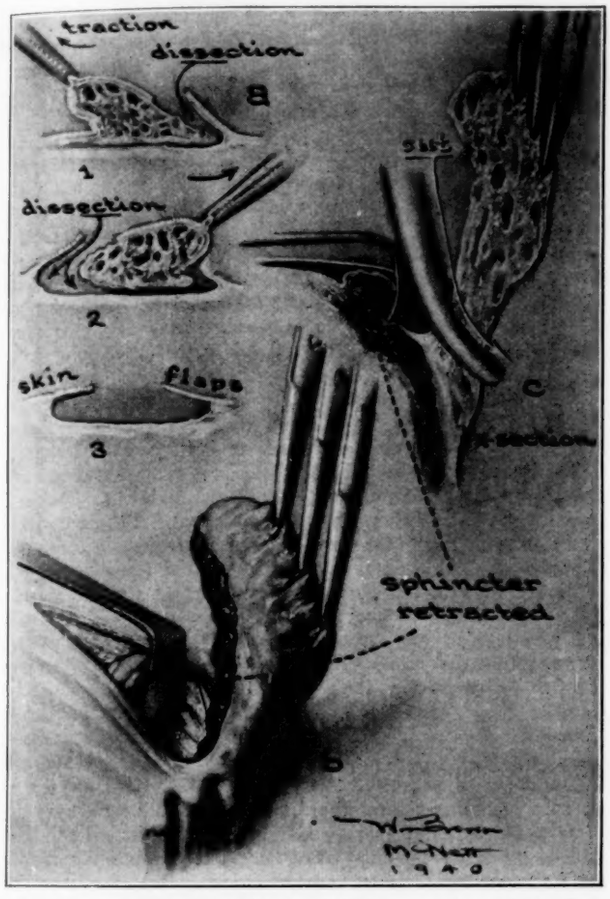


Fig. 3.—*a* 1, manner in which the subcutaneous veins and tissue are separated from anal and perianal skin; *a* 2, posterolateral wall similarly treated; *a* 3, wound after hemorrhoid and all subcutaneous veins have been freed and drawn medialward. *b*, the hemorrhoid and subcutaneous veins have been dissected free on and above the surface of the external sphincter muscle and the latter is retracted. *c*, muscle retractor in place; Smith clamp applied in longitudinal axis. Arrow shows line of incision.

of operation. A Smith hemorrhoidal clamp is placed on the hemorrhoidal mass in the longitudinal axis of the bowel and the hemorrhoid cut away. A suture of no. 0 chromic catgut or no. 00 pyoktannin on a no. 12 Ferguson needle is introduced ¼ inch (0.64 cm.) from the tip of the clamp and tied—the free end to serve as an anchor. The base of the hemorrhoid is then sutured beneath the clamp from side to side. As the anorectal line is approached, the hemorrhoidal clamp is removed and the sphincter muscle permitted to return to its usual location. A subcutaneous bed is formed by continuing the suture to the outer limit of the apex. After all hemorrhoidal masses are treated in a similar fashion, the skin may be approximated distally by means of two or three interrupted sutures of black silk or number 35 alloy steel wire. Where the latter is employed, only a single knot is tied. Ten cc. of a 0.5 solution of diothane hydrochloride is distributed into the substance of the sphincter muscle through a single puncture in the posterior midline behind the anal verge. A cellophane tube drain, of 4 inch no. 14 soft rubber tubing surrounded by a strip of wet cellophane, is introduced, and dressings are applied.

*Postoperative Care.*—Immediately on the patient's return to his room, the foot of the bed is elevated for six hours where a hypobaric (light) analgesic solution is used intraspinally. Liquids, a light soft diet and smoking are permitted. Compresses wrung out in hot boric solution are applied continuously. At night these may be supported by a hot water bottle. Morphine sulfate in ¼ grain (0.01 Gm.) doses is given only if necessary. Blood pressure readings are made every hour for six hours in both arms. Twenty-four hours after operation the cellophane tube drain is removed and an aqueous solution of 1 per cent gentian violet applied on a glass rod. Liquid petrolatum is given by mouth once or twice daily and continued for approximately ten to fourteen days. On the second postoperative day, an enema of warm saline solution or olive oil is administered through a no. 14 soft rubber catheter. Thereafter the patient is permitted out of bed, a house diet is prescribed and sitz baths thrice daily, at a temperature of 110 F. and a depth of 6 inches for ten minutes, are begun. When discharged on the third or fourth postoperative day, the patient is advised to continue with the sitz baths, employ cotton tissue rather than toilet paper and have one daily evacuation. Skin sutures are removed on the fifth to the seventh day, at which time the lubricated gloved finger is introduced.

*Analysis of Cases.*—The degree of postoperative pain in this series was determined by several factors: (*a*) subjective complaint, (*b*) narcotic required, (*c*) ease of first bowel movement, (*d*) need for catheterization and (*e*) digital examination.

Ten hundred and thirty-three operative procedures in the hospital on adults were performed, of which 642 were for hemorrhoids. However, in 416 cases the method of hemorrhoidectomy previously outlined was utilized, and only 32 patients, or 7.6 per cent, complained of severe pain. This number required a mini-

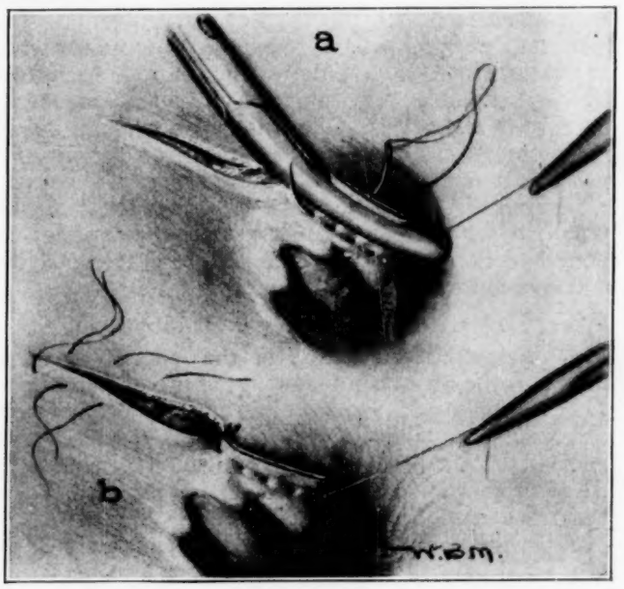


Fig. 4.—*a*, anchor suture placed in mucosa immediately above excised internal hemorrhoid. Suture continued beneath the clamp to anorectal line when clamp is removed. Subcutaneous bed beneath anal and perianal skin is continued. *b*, distal portion of skin is approximated with black silk or number 0.35 alloy steel wire.

mum of two and a maximum of three ¼ grain (0.01 Gm.) doses of morphine. It may be mentioned that 14 of this group were members of the medical profession. Forty-one per cent of the patients complained of considerable discomfort during the first twenty-four

hours, for which a single dose of the narcotic was given. The remaining number, 51.4 per cent, cited discomfort but no pain such as necessitated a narcotic. In the entire group, many patients were restless and insomnolent, for which reason pentobarbital-sodium was prescribed, but no estimation of the number was made. On no occasion did a patient describe pain on removal of the cellophane tube.

Only 12 per cent of the patients in whom a fissure was excised complained of pain; this group required one dose of morphine, ¼ grain (0.01 Gm.).

Considering now the entire group of 1,033 cases, 27 per cent cited pain as such and required a narcotic during the first twenty-four hours; 2 per cent were given morphine the second day. About one-half the number received castor oil by mouth on the third postoperative day, and while accurate statistics have not been completed, practically all experienced moderate to severe pain at the time of the first evacuation. Since a warm saline or olive oil enema through a small soft rubber catheter has been substituted, usually on the second postoperative day, no pain was cited, although varying degrees of discomfort were described at subsequent voluntary movements. The patient, however, being permitted out of bed, sat in hot water immediately.

Urinary retention in a series of 1,126 cases recently reported was computed at 7.1 per cent (81 patients). All, however, did not require catheterization.

Digital examination from the second to the seventh postoperative day was attended by varying degrees of discomfort. No complications, such as abscess formation, from closure of the wound in the perianal skin were encountered, although in each case dead-spacing was prevented by the formation of a subcutaneous bed. The cutaneous wound in most instances healed by first intention, especially where alloy steel wire was employed. The period of convalescence hemorrhoidectomies, including those of the external variety, averaged nineteen days. Worthy of special mention is the fact that almost all patients, exclusive of those for whom a plastic procedure on the sphincter was performed, showed some degree of sphincter muscle atonia, averaging five to eight days. One patient, on whom a hemorrhoidectomy was done, was examined on the fifty-first postoperative day and cited lack of control. The muscle was atonic. When he was seen one week later, the tone had returned to normal. In the gross series, the period of hospitalization postoperatively averaged four and one-fourth days.

## SUMMARY AND CONCLUSIONS

1. Spasmodic contraction of the external sphincter muscle is the important factor in the production of pain.

2. An improved technic of hemorrhoidectomy without trauma to the external sphincter muscle was adopted, based on a series of 416 cases. Of this number, 51.4 per cent cited discomfort but no pain and did not require a narcotic.

3. In the entire series of 1,033 patients only 27 per cent cited pain as such and required a narcotic.

4. Contrary to common belief, wounds of the skin may be sutured without complications, providing a subcutaneous bed is formed. By this method the period of convalescence is reduced.

5. The prolonged use of an analgesic solution has proved of value in this series toward the avoidance of sphincterismus.

6. Meticulous postoperative care and periodic examination thereafter are to be recommended.

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## ABSTRACT OF DISCUSSION

DR. EMIL GRANET, New York: Freedom from postoperative complications and pain depends primarily on technics designed to minimize trauma and infection. For proctologic surgery, epidural caudal block utilizing 30 to 40 cc. of 2 per cent procaine hydrochloride has given ideal anesthesia. Twelve per cent were failures resulting from anatomic abnormalities which prevented adequate deposition of the anesthetic solution. The disagreeable complications of spinal anesthesia, such as headache, vomiting and hypotension, as well as late neurologic sequelae recently described by Brock and others, are avoided by epidural anesthesia. The inverted angle position is comfortable for patient, operator and assistant. The ingenious ring retractor recently described by Hullsieck affords excellent exposure in hemorrhoidectomy and dispenses with the second assistant. One important factor in the mechanism of pain is pressure or tension on sensory nerves. In postoperative wounds, pressure on exposed sensory nerves is induced by increase in tissue tension resulting from edema, inflammation or reaction to tight sutures. To minimize postoperative pain, the operation of hemorrhoidectomy must be designed to eliminate increased tissue tension in the wound. The operation which best fulfils these criteria is a modification of the ligature or open operation first introduced in principle by Mr. Salmon at St. Mark's Hospital, London, over one hundred years ago. In this procedure the hemorrhoid is dissected cephalad, as described by Dr. Bacon. The hemorrhoidal mass containing only varicose veins, redundant rectal mucosa and skin is transfixed and tightly tied above the area of pain sensitivity (the anorectal line). The hemorrhoidal mass is amputated distal to the strangulating ligature, which sloughs off after nine days. The skin wound remains open for drainage, so avoiding tissue tension. Ten cc. of eucupine in oil is radially injected into the sphincter muscle. A thin sliver of petrolatum gauze remains in the wound. Postoperative urinary retention rarely occurs since I have been instilling 30 cc. of 0.5 per cent aqueous solution of mercurochrome into the bladder by catheter immediately after operation. Patients are immediately allowed a full smooth diet. Liquid petrolatum is administered every night. The pack is removed and the patient allowed out of bed after twenty-four hours. Sedation for pain is rarely necessary after the first twelve hours. Eucupine (isoamylhydrocupreine) is released slowly from its oil solution to the tissues, but its antispasmodic effect persists for from ten to fourteen days.

DR. HENRY RAILE, Salt Lake City: I am convinced that the muscle-avoiding technic outlined by Dr. Bacon is a desirable first step for avoiding postoperative pain following hemorrhoidectomy. The fact that the postoperative pain is frequently marked in so common an operation has put fear and dread into the minds of many in need of such attention. I have found that by following a simple postoperative procedure pain is not usually a fearsome necessity. A postoperative congestion in the operative field can be avoided by elevating the buttocks by placing the patient on his abdomen lying across two pillows immediately on his being placed in bed following the hemorrhoidectomy. Spasm of the anal sphincter and its accompanying pain can be avoided by applying at once hot hamamelis water packs for the first four hours, repeating the procedure daily for any beginning spasm. Analgesic oil injected into the anal sphincter muscles is also beneficial. Infection in the area of operation, another too frequent cause of postoperative pain, can usually be avoided by keeping the area scrupulously clean. Follow every defecation with a careful irrigation of warm physiologic solution of sodium chloride or boric acid solution and paint with some antiseptic preparation as merthiolate, metaphen or mercurochrome. An early stool, usually on the second postoperative day, and the maintenance of a soft state of daily stools will aid in avoiding the occasional hard impacted stool, a near catastrophe for the patient.

DR. MALCOLM R. HILL, Los Angeles: The patient's ever present fear and dread of pain which follows anorectal surgery accounts for the frequent neglect of relatively simple problems. The medical profession has taken this problem altogether too lightly and considered it an incompatibility that in due time will correct itself after routine surgical measures are carried out. The author's paper emphasizes fundamental principles of great

importance. Any measure which can be instituted for the immediate relief of postoperative pain following rectal surgery is a worthy consideration. In Dr. Bacon's method it is hoped that in the hands of others it will prove an equally good panacea for the relief of pain. I myself have used several of the oil soluble anesthetic preparations obtainable through the drug trade. The results have not been too uniform. The first consideration in which I differ with Dr. Bacon is in the shaving of the perianal tissues preoperatively. This I believe produces in many cases a folliculitis to be followed by considerable annoyance from the outgrowing hair. Clipping of the hair certainly is adequate. In the second consideration I can see no logical reasoning to the weight-dosage ratio in spinal anesthesia for anorectal surgery. I find 50 mg. of procaine hydrochloride sufficient in the average hemorrhoid case irrespective of weight. I am willing to agree that suturing of perianal tissues in Dr. Bacon's hands is certain to be a success and probably a valuable aid in healing of the parts. However, to advocate the wide dissemination of this method of dealing with perianal tissues certainly will lead to many unsatisfactory results, perianal abscesses, prolonged annoyance and discomfort.

DR. LOUIS J. HIRSCHMAN, Detroit: The preparation of patients is important and so are many of the things used for postoperative relief, but I should like to say a word or two about operative procedures as mentioned by Dr. Bacon. He has correctly stated that the principal cause of postoperative pain in rectal surgery is the contraction of the sphincter muscle. That is very important. We must remember not to divulse the sphincter, particularly when the divulsion is merely a tug of war between the operator and the patient. If the patient is under general anesthesia the operator wins out, but does it at the expense of a torn and overstretched, ecchymosed sphincter. Then the contractions of the sphincter do cause a great deal of pain. Another thing which insults the rectum is the use of postoperative packing. Many surgeons still pack the rectum full of rubber and gauze, and anything else that is handy, and then forget that a peristaltic stimulation is caused by a filled rectum, whether it is by stool or by gauze, and the peristaltic effort to expel this will cause a great deal of pain. I wish to differ with Dr. Bacon in one important matter. Remember that one of the most sensitive organs of the body is the skin. Every stitch we put into it traumatizes it just so much more. Whether one uses wire, silk or linen, every unnecessary needle hole causes unnecessary trauma to the skin and produces postoperative pain. So does the indiscriminate use of so many unnecessary instruments on the skin edges. One should remove rectal lesions with as small an incision as possible and use the sphincter as a purse string. The incisions pull together nicely without suture and one avoids the evulsive, ineffective malalinement. No matter how careful one is during the operation, mucus and bacteria will soil from the wound above, and it is easy for the surgeon to enclose these under his suture line. And as far as the question of postoperative anesthetic solutions are concerned, one must prepare the point of puncture not through the skin but through the raw surface by applying phenol before injecting, so as not to carry infective substances in with the needle. It is not so much the question of preventing postoperative pain as keeping the patient comfortable. Regardless of what else one uses, if the patient needs morphine, give it to him. Keep him comfortable always and the patient won't complain about pain following anorectal surgery.

DR. ARTHUR S. CALMAN, New York: I agree with Dr. Bacon that the foremost consideration in the operation of hemorrhoidectomy is the elimination of pain. But there are other even more important complications which must be avoided, such as injury to the fibers of the external sphincter by overstretching, as was emphasized by Dr. Hirschman. Postoperative hemorrhage and postoperative anorectal stricture must also be prevented. These complications are all due to the employment of the older methods of hemorrhoidectomy, such as the clamp and cautery and the excision with suture methods. I wish to call attention to an operation that I have devised and described recently under the title of submucous hemorrhoidectomy, which eliminates completely all the complications enumerated. I use a 1 per cent solution of procaine hydrochloride locally or a general anesthetic if the patient so desires. I don't stretch the anal sphincter. The assistant brings the operative field in view by gentle manual retraction. I make a small transverse incision at the mucocutaneous junction and undermine the mucosa with a curved Mayo scissors, raising a flap, as in a cystocele operation, along the entire length of the hemorrhoid. A longitudinal incision is made along the midline of the mobilized mucosal flap, exposing the underlying hemorrhoid in its entirety. A suture ligature of number 00 plain catgut, which is absorbed shortly, is then passed around the distal end of the hemorrhoid and ligated. These flaps act like autografts. They agglutinate promptly to the underlying raw surface, thus avoiding scar and stricture formation during the healing process. No secondary hemorrhage can follow this operation, for there are no open granulating areas which could possibly become infected. In dealing with the combined external and internal hemorrhoid I begin with a V shaped incision at the base of the external hemorrhoid instead of a transverse incision at the mucocutaneous line and then proceed as described. I don't have to use more than a quarter of a grain of morphine as soon as the patient recovers from the anesthesia. A tablespoon of liquid petrolatum twice daily will give the patient a painless evacuation, there being no raw area exposed to irritation.

DR. HARRY E. BACON, Philadelphia: I should like to mention the fact that every effort is made to have the patient as comfortable as is possible. I do not spare morphine if it is necessary. I cannot agree with Dr. Granet as to the use of oil-soluble anesthetics. The work is far from completion but I have been able to show histologically that the process of healing is retarded. I believe that Dr. Malcolm Hill misunderstood me, because I do not give the patient morphine immediately after operation. That is done only when it is necessary.

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# STUDIES OF THE PRINCIPLE IN LIVER EFFECTIVE IN PERNICIOUS ANEMIA

## VI. RECENT ADVANCES IN THE PURIFICATION OF ACTIVE SUBSTANCES

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AND
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It is now fourteen years since the original announcement by Minot and Murphy [1] of the effectiveness of liver therapy in pernicious anemia. During this period several groups of workers have attacked the problem of the isolation of the hemopoietically active material. It is fair to say that up to the present no such chemically pure and therapeutically active material has yet been isolated.[2] On the other hand, numerous advances toward this goal have been made, and it is our intent in this communication to summarize the present state of progress.

The history of the isolation from natural sources of biologically active materials, in all probability, reveals no instance replete with the difficulties attending the isolation of the antianemic principle of liver. This unique character of the liver principle is mainly consequent on the fact that for all other biologically active materials there exist satisfactory methods for the assay

This study has been supported by grants from the John and Mary R. Markle Foundation and from Dr. Clarence J. Gamble.

All the liver extract used in this investigation was prepared from material furnished by Lederle Laboratories, Inc., Pearl River, N. Y.

From the Medical Clinic, Massachusetts General Hospital, and the Departments of Medicine and Biological Chemistry, Harvard Medical School.

Read before the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

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of activity in animals, either in the normal state or in an induced pathologic state. The liver principle, on the other hand, in the light of present knowledge, evidences its biologic activity only by its therapeutic effects in pernicious anemia. Despite numerous attempts to find among animals a natural or induced condition in which the entire therapeutic activity of liver might be quantitated, no such proposed test has proved feasible. The guinea pig assay method [3] used by us has yielded valuable information concerning parts of the liver principle but cannot serve as an indicator of the entire therapeutic potency of liver. Thus the fractionation of crude liver into its component parts must depend on the assay of each fraction in patients suffering from a relapse of pernicious anemia. The attendant difficulties of this method of assay need no further amplification.

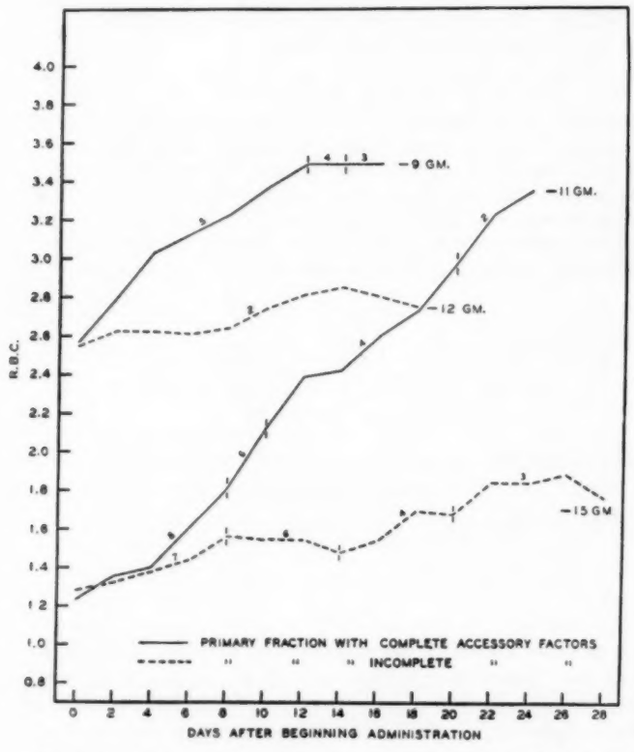


Chart 1.—Averages of erythrocyte regeneration curves following the administration of primary factor with incomplete and with complete complement of accessory factors. The number of patients studied in each period is shown by the small figures above each curve. The quantity at the end of each curve denotes the calculated average daily amount of primary factor administered, expressed in terms of amount of fresh liver from which the extract was derived.

Furthermore, an additional obstacle in the isolation of the liver principle is the apparent loss of therapeutic activity, as the fractionation proceeds, even in the absence of destructive physical or chemical procedures. This apparent loss, which we ascribe to the multiple nature of the liver principle, is discussed more fully later.

## THE GROUNDWORK OF THE PROBLEM

The pioneer work of Cohn, Minot and their collaborators, extending from 1927 to 1930, furnished the basic method of the preliminary attack on whole liver, a starting point of virtually all later workers. Their attack consisted in the removal of the bulk of the liver proteins by means of heat coagulation on the acid side, followed by the removal of additional protein material by means of 70 per cent alcohol, and finally by the precipitation of the greater part of the hemopoietically active substances in the presence of 95 per cent alcohol. This precipitate, the well known fraction G of Cohn,[4] was originally tested in patients with pernicious anemia by means of oral administration and, in doses of approximately 10 Gm. daily, was therapeutically effective.

By 1929, further purification of fraction G, in the hands of Cohn and his collaborators,[5] with the elimination of protein and of depressor constituents, resulted in a product that could be safely injected intravenously. This can be called a notable advance, for by this step there were eliminated the uncertainties of absorption following oral administration and the necessity of dealing with considerably larger quantities of material during the process of fractionation. All subsequent investigators have assayed their materials by means of parenteral administration either intravenously or, more commonly, intramuscularly.

By 1930 Cohn, McMeekin and Minot,[6] utilizing a variety of procedures, obtained a material which, in an injected dose of 140 mg., increased the concentration of erythrocytes of a patient with pernicious anemia by nearly 1,000,000 per cubic millimeter during the following ten days. This most highly purified material, in an amorphous state, had many of the properties of a nitrogenous base.

## PARALLEL TRENDS OF INVESTIGATION

During the five years subsequent to the last communication in 1930 by Cohn,[6] three groups of workers were engaged in the isolation of the liver principle, each utilizing different methods of preparation and each contributing significantly to the process of purification. During the years 1935 and 1936 Dakin and West in New York, Subbarow and Jacobson in Boston and Laland and Klem in Oslo, Norway, published the results of their investigations.

Two important steps in purification were introduced by Dakin and West. In 1935 they [7] described the fact that therapeutically active material could be precipitated from Cohn's fraction G by Reinecke acid, and in 1936 Dakin, Ungley and West [8] showed that from the same source the active material could be brought down by saturated ammonium sulfate. The utilization of each of these procedures, followed by other steps, finally yielded their most highly purified fraction, which exhibited many of the properties of a peptide and which, in doses of from 40 to 100 mg., parenterally administered, was followed in most instances by moderately active therapeutic responses. Similar material in the form of the commercial preparation anahaemin was administered by Ungley, Davidson and Wayne [9] in doses of from 100 to 150 mg. during the first ten days, with resultant moderately active responses.

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8. Dakin, H. D.; Ungley, C. C., and West, Randolph: Further Observations on the Chemical Nature of a Hematopoietic Substance Occurring in Liver, J. Biol. Chem. **115**: 771-791 (Oct.) 1936.

9. Ungley, C. C.; Davidson, L. S. P., and Wayne, E. J.: The Treatment of Pernicious Anemia with Dakin and West's Liver Fraction, Lancet **1**: 349-354 (Feb. 15) 1936.

In 1935 a novel and valuable step was arrived at by three groups of investigators independently of one another. Laland and Klem [10] working with Strandell,[11] Subbarow, Jacobson and Fiske [12] and Kyer [13] found that charcoal quantitatively adsorbs the active liver principle. The Scandinavian workers,[14] furthermore, observed that the active material could be eluted from the charcoal by means of phenol. With these two steps they arrived at considerable purification, with, however, apparent losses in potency. Thus several fractions (VIII, E and BF) reported by Strandell,[11] in average

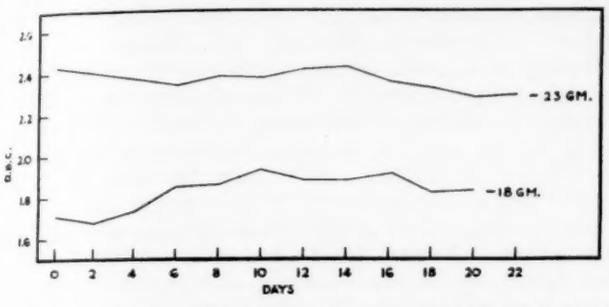


Chart 2.—Average erythrocyte regeneration curves following the administration of five accessory factors (tyrosine, complex purine, peptide, tryptophan, guanosine) without primary factor. The quantity at the end of each curve denotes the calculated average daily amount, in terms of whole liver from which the material was derived, of the fractions administered.

doses of 170 and 54 mg., respectively, during periods of from four to five weeks, showed moderate hemopoietic activity, while a much more highly purified fraction, in an average total dose of 5 mg. during a period of five weeks, showed significantly less activity.

Both the innovations of Dakin and West and of Laland and Klem were utilized in 1936 by Ungley,[15] who treated anahaemin with phenol, followed by methyl alcohol precipitation of active material from the phenolic solution. This precipitate, in average doses of from 34 to 75 mg. per ten days, exhibited moderate therapeutic activity, no greater, however, than similar doses of less purified material used by Dakin, Ungley and West.[8]

In contrast to the Scandinavian workers, both Subbarow, Jacobson and Fiske [16] and Kyer [13] used charcoal for adsorption, followed by alcoholic elution of active material. This method has proved highly successful, always yielding chemically crude extracts maximally active in doses of approximately 140 mg. per ten days, an amount of extract derived from 100 Gm. of whole liver.

Finally from Switzerland there have appeared, in the last three years, reports of further attempts to isolate the liver principle. Karrer, Frei and Fritzsche [17] and Karrer, Frei and Ringier [18] have reported briefly on some properties of highly purified materials, with no description, however, of the method of preparation. Their best material they reported to be active in doses of from 8 to 10 mg.[18] In 1938 Koller [19] presented in detail the assays of preparations furnished him by Karrer. In contrast to the statement by the latter, Koller's data concerning the three most highly purified fractions (extracts 25, 28, 35) administered in initial doses of 20, 15 and 20 mg., respectively, indicated only slight therapeutic activity. After the administration of cruder fractions, however, in an average dose of 19 mg. per ten days, the resultant responses demonstrated moderate activity (chart 4).

### DIVERGENT TRENDS OF INVESTIGATION

It is evident that the accomplishments of the several groups of workers just described have in common a position far short of the goal of the isolation of the liver principle. It is axiomatic that the fulfilment of the quest must be the isolation in pure chemical form of the principle that completely duplicates the therapeutic activity of whole liver. If it is assumed that the liver principle consists of a unitary chemical compound, then it is fair to describe these advances as extremely divergent.

Divergence of trends of investigation had its beginning in the contrasts between the chemical properties described for their purest material by Cohn, McMeekin and Minot in 1930 [6] and those reported by Dakin and West in 1935,[7] and again in 1936 by Dakin, Ungley and West.[8] But in 1935 Fiske, Subbarow and Jacobson [20] branched off on a new path with their hypothesis

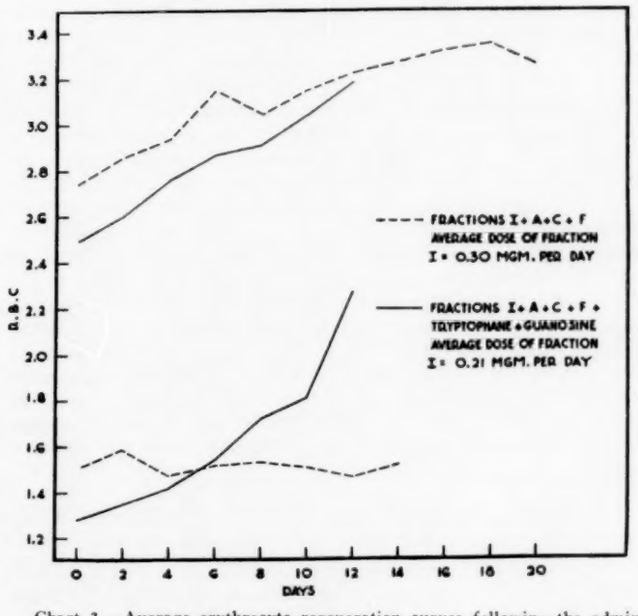


Chart 3.—Average erythrocyte regeneration curves following the administration of purified primary factor (fraction I) with three accessory factors and with five accessory factors.

of the multiple nature of the liver principle. The evidence for this view was further presented by Subbarow and Jacobson [21] in 1936 and more completely

10. Laland, Per, and Klem, Aage: Experiments to Isolate the Antianemic Principle of the Liver: Chemical Part, Acta med. Scandinav. **88:** 620-623 (May 27) 1936.
11. Strandell, Birger: Experiments to Isolate the Antianemic Principle of the Liver: Clinical Part, Acta med. Scandinav., 1935, supp. 71, pp. 1-52.
12. Subbarow, Yellapragada; Jacobson, B. M., and Fiske, C. H.: The Separation of the Substances in Liver Which Are Reticulocytogenic in the Guinea Pig and Which Are Therapeutically Effective in Experimental Canine Blacktongue, New England J. Med. **212:** 663-664 (April 11) 1935.
13. Kyer, Jean L.: Charcoal Adsorption As a Method for the Preparation of Concentrated Liver Extract, Proc. Soc. Exper. Biol. & Med. **32:** 1102-1103 (April) 1935.
14. Laland and Klem.[10] Strandell.[11]
15. Ungley, C. C.: Further Purification of Dakin and West's Liver Fraction; Purified Anahaemin Compared with Original Product in Regard to Effect in Pernicious Anemia, Lancet **2:** 1513-1518 (Dec. 26) 1936.
16. Subbarow, Yellapragada; Jacobson, B. M., and Fiske, C. H.: A Partially Purified Liver Extract Therapeutically Effective in Pernicious Anemia, New England J. Med. **214:** 194 (Jan. 30) 1936; footnote 12.
17. Karrer, Paul; Frei, P., and Fritzsche, H.: Ueber einen Bestandteil von gegen Perniziöseanämie hoch aktiven Leberpräparäten, Helvet. chim. acta **20:** 622, 1937.
18. Karrer, Paul; Frei, P., and Ringier, B. H.: Bestandteile von gegen Perniziöseanämie hoch aktiven Leberpräparäten, Helvet. chim. acta **21:** 314-315, 1938.
19. Koller, F.: Ueber die klinische Wirksamkeit hochkonzentrieter Leberextrakte, Deutsches Arch. f. klin. Med. **183:** 296-314, 1938.
20. Fiske, C. H.; Subbarow, Yellapragada, and Jacobson, B. M.: The Multiple Nature of the Pernicious Anemia Principle in Liver, J. Clin. Investigation **14:** 709 (July) 1935.
21. Subbarow, Yellapragada, and Jacobson, B. M.: Chemical Studies of the Pernicious Anemia Principle in Liver, J. Biol. Chem. **114:** ciiciii (May) 1936.

amplified in 1937.[22] Early in the course of our work certain observations suggested the possibility that the therapeutic activity of liver extract might depend on the presence of several distinct substances.[20] The observations comprised a body of indirect evidence that need not concern us at present. The direct evidence for the multiple factor hypothesis was the fact that continued purification of crude liver extract, in the absence of significant losses and of destructive procedures, resulted in partial or complete extinction of therapeutic activity. But the admixture with such purified materials of other fractions derived from liver resulted in the recovery of therapeutic activity.[22] The latter fractions have been termed accessory factors, for, while by themselves therapeutically inert, they appeared to augment the activity of the primary factor (or factors) contained in the purified fractions.[22]

Up to 1938 there were isolated from crude liver extract three distinct materials considered to act as accessory factors. These were *l*-tyrosine (fraction A) [12] in a yield of 6 mg. from 100 Gm. of whole liver, a complex purine (fraction C) [12] in a yield of 11 mg., and a peptide (fraction F) [21] in a yield of 14 mg.

In 1938 Sladek and Kyer [23] described the preparation of an alcoholic elute of charcoal adsorption with properties very similar to such an elute described by us in 1936.[16] Sladek and Kyer state that they discard the complex purine which separates out after concentration of the elute, since "the concentrate from which it is filtered has shown satisfactory hematopoietic activity." Well it might, for this filtrate, as noted diagrammatically by us,[22] still contains a significant amount of the purine. Furthermore, Sladek and Kyer describe the presence of tyrosine in their charcoal adsorbate and refer to us [12] as stating that the tyrosine is to be found in the charcoal filtrate. On the contrary, although "the solution was decolorized with a small amount of charcoal," [12] this amount is insufficient to adsorb any significant quantity of tyrosine. Norit charcoal,[16] when used in an adequate amount, has always quantitatively adsorbed the tyrosine present in crude commercial liver extract.

The resemblance of this purine to the type of compound known as pterine, of which an example is xanthopterine, the pigment of the wings of yellow butterflies, was pointed out in 1935.[12] It is of interest that in a search for the factor in liver curative of goat's milk anemia in rats, Tschesche and Wolf [24] obtained high concentrations of the factor in purine fractions of liver extract and also in similar fractions of human urine. In view of the isolation by Koschara [25] from urine of a pterine, designated by him uropterine, probably identical with xanthopterine from butterflies' wings, Tschesche and Wolf assayed both materials in pure form of their activity in goat's milk anemia and found them strongly curative in doses as small as 0.5 microgram a day. A similar activity was shown by a substance prepared from liver and identical with the complex purine of ours.

Crude sources of primary factor were obtained by us by means of alcohol-ether precipitation on the previously described alcoholic elute of charcoal adsorption.[26] Such sources of primary factor were described as fraction H, derived from a fuller's earth filtrate on the alcoholic elute and obtained in a yield of 20 mg. from 100 Gm. of whole liver,[22] and fraction E, derived directly from the alcoholic elute, in a similar yield of 20 mg.[22] These two materials differed from each other only in the fact that fraction E contained minimal amounts of the accessory factors while fraction H was almost entirely devoid of these substances. It was first demonstrated in eleven experimental periods among 9 patients with pernicious anemia that the accessory factors, singly or in combination, were entirely inert.[22] Then, in nine experiments it was shown that the sources of primary factor, either alone or when administered together with any two of the three accessory factors, exerted either no hemopoietic effect whatever or an ill sustained, slight effect.[22] Finally, the combination of all three accessory factors with either of the sources of primary factor, in thirteen experiments, induced responses indicating moderate therapeutic activity. In chart 1 are reproduced from a previous publication [22] averages of such erythrocyte regeneration curves, demonstrating in a clear-cut fashion the augmentative action of the accessory factors on that of the primary factor. In chart 4 it is evident that the particular dosage administered of this combination of factors approximates, but does not equal, the effect induced by an amount of commercial liver extract [27] derived from a similar quantity of whole liver (compare the Jacobson and Subbarow 1937 curve with the Murphy-Hartfall curve).

It should be emphasized that this augmentative action of the accessory factors does not depend on additive effects of a substance common to all, for the accessory factors, in the absence of primary factor, were administered in large dosage, with no resultant response whatever.[22]

It was pointed out in 1937 [22] that all possible accessory factors in crude liver extract might not be represented by only tyrosine, the complex purine and the peptide. In 1938 Subbarow, Jacobson and Hartfall [28] isolated from fraction H two substances in a pure state and identified them as tryptophan and guanosine respectively. The former was obtained in a yield of 8 mg. and the latter in a yield of 5 mg., respectively, from 100 Gm. of whole liver. Certain indirect evidence suggested the possibility that these substances might act as additional accessory factors. In the absence of primary factor they too exert no therapeutic effect, even in the presence of the other three accessory factors. In chart 2 are depicted the results of the administration of large amounts of each of the five substances together in twelve experiments among eleven different patients with pernicious anemia. The average curves of erythrocyte regeneration over a period of twenty days included all cases, but in eight cases the periods of observation were considerably longer, ranging from thirty-seven to forty-four days. These data amplify the previously reported results after the administration of only fractions A, C and F [22] and demonstrate clearly that the five accessory factors together, in the absence of primary factor, are completely devoid of therapeutic action.

Finally, the additional augmentative effect exerted by tryptophan and guanosine together is indicated by the data in chart 3.[29] In these experiments the source of the primary factor was a more highly purified material,

22. Jacobson, B. M., and Subbarow, Yellapragada: Studies of the Principle in Liver Effective in Pernicious Anemia: IV. The Therapeutic Activity of Its Multiple Factors, J. Clin. Investigation **16:** 573-585 (July) 1937.

23. Sladek, Jaromil, and Kyer, Jean: Preparation and Properties of the Charcoal Adsorbate of Liver Extract, Proc. Soc. Exper. Biol. & Med. **39:** 227-230 (Nov.) 1938.

24. Tschesche, R., and Wolf, H. J.: Ueber den Ziegenmilchanämie-Faktor von Rominger und Bomskov, Ztschr. f. physiol. Chem. **244:** 1-3, 1936; Die Wirkung der Pterine und einiger anderer Stoffe auf den Blutbild diätanämischer Jungtiere und ausgewachsener Ratten, ibid. **248:** 34-40, 1937.

25. Koschara, W.: Isolierung eines gelben Farbstoffe (Uropterin) aus Menschenharn, Ztschr. f. physiol. Chem. **240:** 127-151, 1936.

26. Subbarow, Yellapragada; Jacobson, B. M., and Prochownick, V.: Studies of the Pernicious Anemia Principle in Liver: III. The Isolation and Properties of a Substance with Primary Therapeutic Activity, J. Am. Chem. Soc. **58:** 2234-2236, 1936.

27. One cc. Concentrated Solution Liver Extract Parenteral-Lederle, N. N. R.

28. Subbarow, Yellapragada; Jacobson, B. M., and Hartfall, S. J.: Studies of the Principle in Liver Effective in Pernicious Anemia: V. Additional Accessory Factors and Further Properties of the Primary Factor, J. Clin. Investigation **17:** 517 (July) 1938.

29. Dr. George V. LeRoy of the University of Chicago carried out the assay of these materials in one patient.

fraction I,[26] and was administered with fractions A, C and F to 8 patients and together with all five accessory factors to 8 other patients. The amounts of primary factor administered in both series of experiments were small (0.30 mg. a day, and 0.21 mg. a day, respectively) in order to render more apparent any additional augmentative action of tryptophan and guanosine. Such an action seems to be indicated by the contrasting rates of erythrocyte production, but only at initial erythrocyte levels less than 2 million per cubic millimeter. Is it possible that this difference between the responses of patients at widely different erythrocyte levels indicates more of a deficiency of the latter two substances in patients at the lower level? At present we possess no further data bearing on this interesting possibility.

The results suggesting the additional augmentative effect exerted by tryptophan and guanosine are the basis for our use, during the past three years, of all five factors in the assay of various materials for their activity as primary factor. In other words, the accessory factors, usually administered in doses of material derived from 10 to 20 Gm. of whole liver a day (4.4 to 8.8 mg. of solids), have been maintained constant, while the only variable in our assays has been the nature and the amount administered of various fractions containing primary factor.

### A POSSIBLE UNIFICATION OF DIVERGENT TRENDS

Our multiple factor hypothesis [22] is not shared by the other workers in the field. On the other hand, so long as the liver principle remains in the present impure, noncrystalline state, in the hands of all investigators, every therapeutically active preparation is a mixture of several different substances. This fact is borne out by the extreme variation of the amounts of preparations of different workers that are required to evoke similar therapeutic responses, a degree of variation not attributable to such biologically active pure substances as thiamine, riboflavin, nicotinic acid or ascorbic acid. A consideration of these different therapeutic responses in pernicious anemia may explain some of the discrepancies.

It has long been our belief that preparations derived from liver, when administered in adequate dosage, can be termed active only when they duplicate the action of crude liver extract; that is, when they induce the usual clinical response that is always accompanied by a satisfactory rate of regeneration of erythrocytes. The quantitative measure of therapeutic activity on which we place most emphasis is the rate of erythrocyte regeneration rather than the height of the reticulocyte response. Although the reticulocyte response alone, early in the course of an assay, may indicate qualitatively the presence of active material, and under certain conditions may aid in the evaluation of the comparative potency of two different materials,[30] it can hardly serve as a quantitative measure of the therapeutic activity induced by liver extract. Schiødt [31] has recently clearly demonstrated in a number of cases at different initial erythrocyte levels, cases under treatment with similar amounts of a commercial liver extract, that the height of the reticulocyte peak is related to the initial erythrocyte level rather than to the rate of regeneration of erythrocytes.

How long a period of observation of the rate of rise of erythrocytes is adequate for correct evaluation of a preparation? Although ideally the material to be assayed might be administered until the patient has attained a complete remission and normal level of erythrocytes and of hemoglobin, such a prolonged period of assay is rarely feasible, and we have usually attempted to construct an erythrocyte regeneration curve over a period of at least twenty days.[32] By statistical methods, Schiødt [31] has determined that the rate of rise of erythrocytes during the initial period of twenty days can serve as a valid indicator of the slope of the complete curve of erythrocyte production.

In chart 4 is presented a comparison of the erythrocytogenic activities of various preparations already discussed. Each curve has been constructed from the data contained in the publications of the several authors and represents the average of the responses of a number of patients, almost all at initial erythrocyte levels between 1.00 and 1.99 million per cubic millimeter. The dosage of materials administered has been calculated in terms

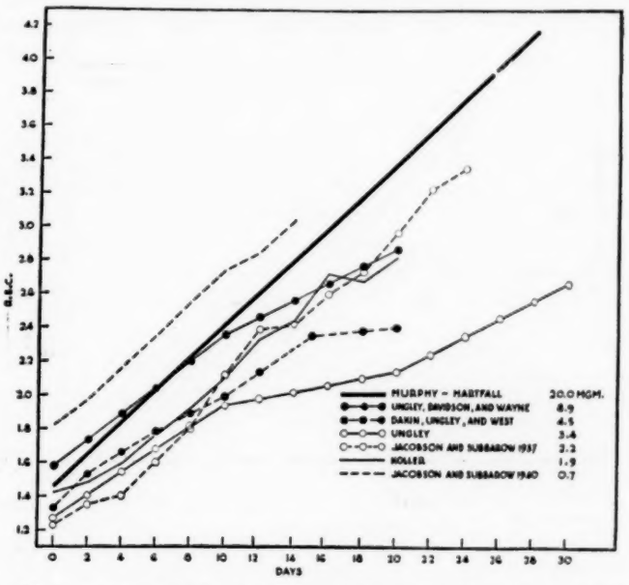


Chart 4.—Average erythrocyte regeneration curves following the administration of various purified liver extracts. The calculated average daily amount of material administered is recorded in the legend. The sources of these data are contained in the text. (The daily doses recorded for the curves of Jacobson and Subbarow refer only to the amount of primary factor administered; in addition, three accessory factors were administered in the 1937 curve, in a daily amount of 3.4 mg. and five accessory factors were administered in the 1940 curve in a daily amount of 6.2 mg.)

of the amount administered per day and is appended to chart 4. Finally, in order to facilitate comparison with a maximal rate of erythrocyte regeneration there has been depicted the rise induced by a moderate dosage of commercial liver extract.[33] This curve has been constructed from combined data taken from the protocols of Murphy [34] and of Hartfall.[35]

From chart 4 it is evident that the hemopoietic activity of each of the purified materials falls short of that of the crude commercial liver extract but that this rate of erythrocyte regeneration is most closely approximated by our 1940 curve induced by material to be described

30. Minot, G. R., and Castle, W. B.: The Interpretation of Reticulocyte Reactions: Their Value in Determining the Potency of Therapeutic Materials, Especially in Pernicious Anemia, Lancet **2**: 319-330 (Aug. 10) 1935.

31. Schiødt, E.: Observations on Blood Regeneration in Man: IV. The Rise in Red Blood Cells in Pernicious Anemia After Specific Treatment: Attempt to Institute a Standard for Valuation of Treatment, Acta med. Scandinav. **98**: 449-467, 1939.

32. The methods used in such an assay have been described previously.[22]

33. One cc. Concentrated Solution Liver Extract Parenteral-Lederle, N. N. R., administered in an average daily dose of 0.14 cc., containing 20 mg. of solids, derived from 14 Gm. of whole liver.

34. Murphy, W. P.: Treatment of Pernicious Anemia with Intramuscular Injections of a Highly Concentrated Solution of Liver Extract, Am. J. M. Sc. **191**: 597-607 (May) 1936.

35. Hartfall, S. J.: Experiences with a Concentrated Whole Liver Extract, Lancet **2**: 317-321 (Aug. 7) 1937.

and administered as primary factor in an average dose of 0.7 mg. a day (together with the five accessory factors in an average total dose of 6.2 mg. a day). Less satisfactory, but nevertheless indicative of good activity, are the three curves of Ungley, Davidson and Wayne, of Koller and of Jacobson and Subbarow, 1937. Definitely less activity is indicated by the curves of Dakin, Ungley and West and of Ungley.

In chart 4 it is to be noted that the curves of Ungley, Davidson and Wayne and of Dakin, Ungley and West, based on the administration of similar material [9] in daily doses of 8.9 and 4.5 mg. respectively, differ significantly from one another, and even the larger dose does not induce the maximal response. This may mean that a major portion of Dakin, Ungley and West's preparation consists of inert material with a relatively small content of active substances or, on the basis of the multiple factor theory, that the preparation contains a relatively small amount either of primary factor or of all accessory factors. A similar interpretation can be given to the material administered by Ungley. Koller's curve, based on a dose of only 1.9 mg. a day, indicates good activity, but this rate of erythrocyte regeneration is nevertheless

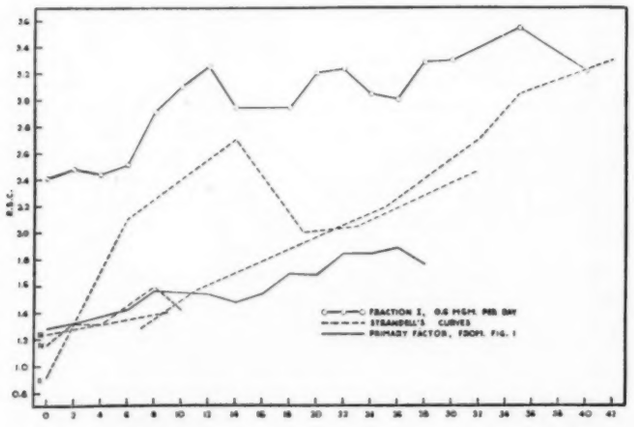


Chart 5.—Erythrocyte regeneration curves following the administration of primary factor.

slower than that of Jacobson and Subbarow, 1940, following the administration of only 0.7 mg. a day in addition to accessory factors. That the material represented by Koller's curve (material furnished by Karrer and his associates,[36] despite its activity in relatively small dosage, consists of more than one substance is implied by Koller,[19] who states that his fractions numbered 25, 28 and 35 are the most highly purified, containing no traces of phosphorus or pentose. None of these fractions are represented in Koller's curve depicted in chart 4. It is of interest, in connection with the multiple factor theory, to note the responses reported by Koller to the administration of these most highly purified fractions. Thus, after the administration of 20 mg. of fraction 25 the erythrocytes rose in twenty days from 3.0 to 3.4 million; in a case under treatment with 15 mg. of fraction 28, the erythrocytes numbered 2.6 million initially and after twelve days 2.5 million; and following the administration of 18 mg. of fraction 35 the erythrocytes rose in six days from 1.4 to 1.8 million. Excluding the latter case, which was observed for an insufficiently long period, it is evident that in the cases tested by Koller the purest preparations of Karrer and his associates were therapeutically virtually inert. It appears likely, therefore, that the limiting factor in Karrer's preparations is the absence of an optimal amount of accessory substances.

Mention is made later in this paper of the most highly purified material described by Laland and Klem [10] obtained in a yield of 0.35 mg. from 100 Gm. of whole liver. Laland and Klem state that a good antianemic effect was observed by Strandell and his collaborators [37] after the injection of only 0.7 mg. This interpretation is not shared by us, for the data of Strandell furnish evidence of only slight to moderate therapeutic activity. The erythrocyte regeneration curves in the four cases under treatment by Strandell are portrayed in chart 5. Although each of these cases exhibited a moderate rise of reticulocytes, the erythrocyte production was moderately submaximal in case 1, markedly submaximal in case 2 and virtually absent in cases 3 and 4.

In chart 5, in addition to these four curves, there is reproduced the lower curve of chart 1, portraying the slight effect on erythrocytes of a moderate dosage of crude primary factor without adequate amounts of accessory factors, and also a curve of erythrocyte regeneration in a case previously reported (case 23 [26]). In the latter case a large amount of relatively pure primary factor (fraction I) was administered in an average dose of 0.6 mg. a day, without accessory factors, over a period of forty days. It is evident that the initial rise of erythrocytes in this instance is limited to the first ten days and that thereafter no further change took place. Of the same order of magnitude are the slopes of Strandell's curves in chart 5. All these curves appear typical of the action of primary factor without accessory factors and certainly do not reproduce the action in pernicious anemia of crude liver extract.

It seems to us, therefore, that the variations in the results of the several groups of workers may depend in part on quantitatively and possibly also qualitatively differing complements of accessory factors contained in the preparations. That only the substances described by us as accessory factors may exert such an action is not established. That other substances present as contaminants in many preparations may act in this fashion is possible.

Finally, the multiple nature of the liver principle, as elaborated by us, has found numerous analogies in the advances in nutritional physiology during the last decade. This concept is well illustrated by the recent observations of Subbarow and Trager [38] that essential accessory growth factors required by mosquito larvae include, in addition to other factors, such chemically unrelated substances as thiamine, riboflavin, pantothenic acid and vitamin $B_6$.

## RECENT STUDIES OF THE CHEMICAL PROPERTIES OF THE LIVER PRINCIPLE

In the published reports of the most highly purified materials in recent years there have been described both concordant and discordant properties. In 1930 Cohn, McMeekin and Minot,[6] on the basis of the properties of their best material therapeutically active in an initial dose of 140 mg., concluded that "the very small amount of α-amino nitrogen suggests that one is not dealing with an α-amino acid but with an ω-amino or imino-acid. The low nitrogen content appears to exclude purine or pyrimidine bases but not ring compounds of

36. Karrer, Frei and Fritzsche.[17] Karrer, Frei and Ringier.[18]

37. Strandell, Birger; Poulsson, L., and Schartum-Hansen, H.: Experiments to Isolate the Antianemic Principle of the Liver: Clinical Part, Acta med. Scandinav. **88:** 624-625 (May 27) 1936.

38. Subbarow, Yellapragada, and Trager, W.: The Chemical Nature of Growth Factors Required by Mosquito Larvae: II. Pantothenic Acid and Vitamin $B_6$, J. Exper. Med. **23:** 561-568 (May 20) 1940.

pyrrole or pyridine types, though the purest fractions do not give the pine-splinter test characteristic of pyrroles." Opposed to this characterization is the conclusion reached in 1936 by Dakin, Ungley and West [8] on the basis of the properties of their best material, moderately active in an average dose of 45 mg. per ten days (chart 4), "that the hematopoietic substance in liver is, or is associated with, a peptide, possessing many but by no means all of the properties of an albumose."

This peptide may or may not be identical with the peptide obtained as a crystalline rhodanilate and reineckate in 1936 by us [21] and described as fraction F, an accessory factor.[22] In our hands this pure peptide, when administered without a source of primary factor in cases of pernicious anemia has been therapeutically inert, as previously described.

In 1939, Dakin and West [39] reported further evidence for the peptide nature of the substance described by them in 1936,[8] by virtue of the fact that it could be partially brought down by a variety of typical albumose precipitants, such as nucleic acid, bile and taurocholic acid, with satisfactory therapeutic activity induced in one case by 30 mg. of such material.

By means of a series of procedures taken from almost all previous workers in the field, Mazza and Penati [40] obtained highly purified material containing a pterine and a polypeptide in combination with adenine nucleotide. The significance of this material is obscured by the fact that it was derived from a cruder fraction (B), described by these authors as therapeutically active but which, on the basis of the data at hand, was virtually inert.

Differing considerably from these two descriptions are the properties described in 1936 by both Laland and Klem and by Subbarow, Jacobson and Prochownick. Laland and Klem [10] proceeded from their material described in 1935 by Strandell [11] by means of further charcoal adsorption, phenol elution and salting out with ammonium sulfate and finally obtained material in a yield of 0.35 mg. from 100 Gm. of whole liver. Subbarow and his collaborators [26] proceeded from their previously described ethyl alcohol elute [16] by means of the removal of inert material with fuller's earth, precipitation with Reinecke acid, following the procedure of Dakin and West,[7] regeneration of the Reinecke precipitate with amyl alcohol extraction, finally bringing down, with a mixture of acetone and ether, a preparation (fraction I) in a yield of 2 mg. from 100 Gm. of liver. The therapeutic activities of these two products have already been discussed, and it has been pointed out that each appears to act as a primary factor. Both of these materials exhibit a degree of concordance unparalleled in the literature, for the properties show similarities in elementary composition and in one point of inflection of the absorption spectrum in the ultraviolet.

Differing in properties from those of all the purified materials discussed are the preparations briefly described by Karrer, Frei and Fritzsche in 1937,[17] by Karrer, Frei and Ringier in 1938 [18] and assayed by Koller in 1938.[19] These authors make no mention of the method of preparation. The therapeutic activity of their material has already been discussed.

In 1936, Wilkinson [41] reported the use of Reinecke acid in the purification of active material, with no description, however, of the method of preparation. The purest material was administered to three patients in doses of 18, 27 and 36 mg., respectively, with resultant initial responses indicative of moderate activity, but neither patient was observed long enough to permit a satisfactory evaluation of the therapeutic potency.

In 1938 Subbarow, Jacobson and Hartfall [28] reported that a derivative of fraction I exhibited chemical properties suggestive of a complex pyridine compound. Further evidence for the pyridine ring as a part of the primary factor was furnished by the fact that moderate therapeutic responses in two cases were induced by the parenteral administration of synthetic nicotinic acid amide in a dosage of 1 and 2 mg. a day, respectively, together with three accessory factors (tyrosine, complex purine and peptide). Finally, during the past year and a half we have modified our method of preparation with resultant improvement in the yield of therapeutically active primary factor.[42] From the alcohol elute the primary factor has been precipitated out by means of Reinecke acid, the regenerated reineckate has been treated with charcoal and then, after the procedure of Laland and Klem,[10] the adsorbate has been eluted with phenol. Further treatment of the phenol elute with various organic precipitants has yielded amorphous materials in quantities of approximately 3 to 10 mg. of organic solids from 100 Gm. of whole liver, with excellent therapeutic activity as primary factor among four patients in an average dosage of 7 mg. per ten days (chart 4).

This, then, is the present known status of the liver principle. Both differences and similarities in methods of preparation and in properties of amorphous materials have been described by various workers during the past four years. Until the primary factor is obtained in crystalline form, this discordant state will exist. Although progress during the last decade has been discontinuous, the trend of investigation augurs the attainment of the goal in the not too distant future.

## ABSTRACT OF DISCUSSION

DR. RANDOLPH WEST, New York: There are certain points that should be emphasized, and one is that the mixture of peptides described by Dakin and later independently by Karrer in Switzerland does not contain any of the accessory factors mentioned. The best preparations of the peptides give no bands in the ultraviolet, and the amino acids isolated from these peptides do not give any either. None of the ring acids are present, tyrosine is not present, no pterins are present, no purines are present, so, whatever the effect of these other substances, they are not the substances which have to do with the essential chemical lesion in pernicious anemia. They may accentuate the action of the essential substance in pernicious anemia, but it is important that attention be focused on the substance which actually has to do with the essential chemical lesion in pernicious anemia, and the best available work shows that this is a mixture of peptides by no means chemically pure, but certainly not containing any of the other substances. I think that in orienting future chemical work a careful analysis of the peptide mixtures by modern methods, the ultracentrifuge, dialysis, electrophoresis and other methods of that sort, are imperative, and I am quite sure that while the substances described are accurately described by Dr. Subbarow and Dr. Jacobson and may accentuate the effect of the essential materials missing in pernicious anemia, they in themselves have nothing directly to do with the chemical lesion in pernicious anemia. We must attack the center of the problem and not the periphery.

DR. BERNARD M. JACOBSON, Boston: We agree with Dr. West that we are focusing our attention on the factor in liver that does the trick in pernicious anemia or, in our terms, the primary factor. Whatever disagreement there may be between our group and other groups on the role of the accessory factors in completing the hemopoietic and clinical response to liver extract, we do not disagree on the necessity for the isolation

39. Dakin, H. D., and West, Randolph: A Hematopoietic Substance in Liver, Proc. Soc. Exper. Biol. & Med. **40**: 124-126 (Jan.) 1939.

40. Mazza, F. P., and Penati, F.: Sulla natura chimica del principio antipernicioso del fegato, Arch. di sc. biol. **23**: 443-471 (Oct.-Dec.) 1937; Nota II, ibid. Arch. di sc. biol. **24**: 83-88 (Feb.) 1938.

41. Wilkinson, J. F.: Note on the Antianemic Principle of Liver, Lancet **1**: 354-356 (Feb. 15) 1936.

42. The details of the method of preparation will appear in a forthcoming publication.

in pure chemical form of the primary or principal liver factor. Up to the present, unfortunately, there still exists a good deal of disagreement between the properties of the factor reported by Klem in Oslo, by Dakin and West in New York, by Karrer in Zurich and by our group in Boston. On the other hand, as long as we are all dealing with admittedly amorphous materials these difficulties will continue to exist and will be abolished only after materials are obtained in pure crystalline state.

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# CEREBRAL SPASTIC PARALYSIS

## THE OBSTETRIC HISTORY OF ONE HUNDRED AND EIGHTY-FIVE CASES

GERALD W. GUSTAFSON, M.D.
AND
GEORGE J. GARCEAU, M.D.
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This study of the obstetric history of 185 cases of cerebral spastic paralysis was undertaken without preconceived ideas as to the most important etiologic factors involved. Schreiber [1] expressed the belief that apnea is the biggest single factor in the production of cerebral injury. He stated that analgesic drugs, given in greater amounts than the pharmacologic dosage, may, in many instances, be the causative factor of fetal anoxemia with resultant cerebral damage in the infant. Cole and his associates [2] stated that prematurity is the most important factor in the etiology of neonatal asphyxia. Other well recognized factors are the normal forces of labor, oxytocics, operative intervention, nonintervention, postnatal infection and trauma in the baby. As the majority of cases of cerebral spastic palsy are associated with definite cerebral injury at birth, we thought it worth while to review the obstetric histories of a group of children with this disorder.

*Material.*—It seemed most logical to take advantage of the patients available in the cerebral spastic palsy clinic at the James Whitcomb Riley Hospital for Children of the Indiana University Medical Center. Therefore a history was taken from the mothers of 185 of these patients. Obviously, the amount of information and various details was not as complete as could be obtained by delving into thousands of hospital obstetric records to obtain a similar number of cases; nevertheless, the salient features of each case are present and we are dealing with known facts and not a hypothesis. We feel confident of the accuracy of the data here submitted. Twenty-three infants (12.4 per cent) were delivered in hospitals, while 162 (87.6 per cent) were delivered in homes. Analgesia and anesthesia played little if any part in this series. Of those delivered at home, an occasional injection of morphine and a small amount of ether were given, the majority of the mothers being awake at or shortly after delivery. In no case did there seem to be any relationship between analgesia or anesthesia and the etiology of the condition. This series, then, seems to constitute a cross section of American obstetric cases in which cerebral injury occurred in the infant though labors were conducted without or with a small amount of analgesia and anesthesia. In only 1 child was there a positive Wassermann reaction. The mother of another was syphilitic but had been adequately treated, and her baby's Wassermann reaction was negative. There were 8 patients in whom the lesion appeared to be due to postnatal infection or trauma.

In 18 children no definite cause could be found. We hold the opinion that some of these lesions are probably developmental in nature. We realize the lack of evidence. Necropsy would be necessary to defend this opinion.

*Age and Parity of the Mothers.*—The age of the mothers is given in chart 1. The greatest number of cases, namely 60, or approximately 32 per cent, occurred in labors of women between the ages of 20 and 25, while only 7 children, or 3.7 per cent, had mothers between the ages of 40 and 45. The parity of the mothers is shown in the table. We would expect to find the largest number of injuries in infants of primiparas, and such is the case, as 106 of the injured infants were first born. After the third child the incidence of cerebral injury is much lower. Boys, because of their slightly larger size, are more prone to injury, our statistics showing 108 boys to 77 girls in the series.

*Length of Labor.*—Chart 2 shows the length of labor of the mothers. That other factors are present in addition to the forces of labor is shown by the fact that 3 mothers had no labor but were delivered by elective cesarean section. One of these mothers had an attempted induction of labor with thirteen "shots" plus castor oil and quinine before the section was performed. The occurrence of cerebral injury in the baby after cesarean section has been reported by other authors.

Precipitate labor was found in six instances, while the greatest number of mothers required labor of from only one to six hours. Apparently there is an increased tendency to cerebral injury in the children of mothers having less than twelve hours of labor.

*Duration of Pregnancy.*—There were 125 babies delivered at full term while 5 were thought to be post mature. Fifty-five infants or 30 per cent were definitely premature. It has been recognized for some time that in the premature baby, with its fragile blood vessels, cerebral injury is more likely to develop. This study emphasizes that the prevention and management of the premature labor is one of the essentials in the prevention of cerebral injury in the newborn.

*Distribution of Parity*

| Parity of Mother | No. of Cases |
|---|---|
| I | 106 |
| II | 29 |
| III | 27 |
| IV | 8 |
| V | 3 |
| VI | 4 |
| VII | 2 |
| VIII | 3 |
| IX | 1 |
| X | 1 |
| Unknown | 1 |

Type of delivery is illustrated in chart 3. In those cases in which presentation was known, there were one hundred and sixty-three vertex, three face and seventeen breech presentations.

*Mature and Postmature Group.*—Included in these were eighty-two spontaneous deliveries, thirty-two forceps deliveries, thirteen breech deliveries (including forceps on the after-coming head in 2 cases) and three cesarean sections. One of the cesarean sections was

From the Departments of Obstetrics and Orthopedic Surgery, Indiana University School of Medicine.
Read before the Section on Obstetrics and Gynecology at the Ninety-First Annual Session of the American Medical Association, New York, June 13, 1940.

1. Schreiber, Frederic: Apnea of the Newborn and Associated Cerebral Injury: Clinical and Statistical Study, J. A. M. A. **111**: 1263-1269 (Oct. 1) 1938.
2. Cole, W. C. C.; Kimball, David C., and Daniels, L. E.: Etiologic Factors in Neonatal Asphyxia, J. A. M. A. **113**: 2038-2044 (Dec. 2) 1939.

performed two weeks after the calculated date for delivery. One patient was born by cesarean section after the mother had had several hours of labor and was several weeks past her calculated date for delivery. Definite spells of cyanosis were present from birth. The third section in this group was done after fourteen hours of labor. Here no resuscitation was necessary, and no cyanosis was present.

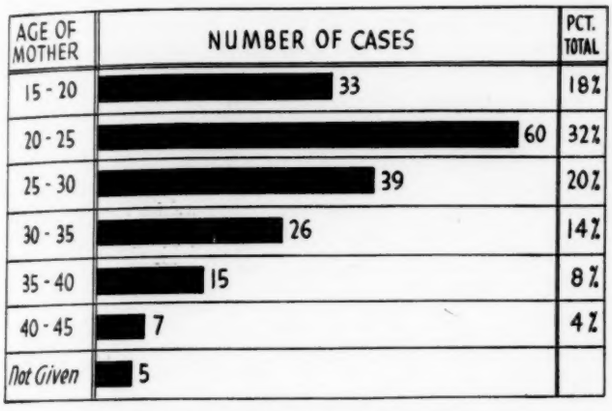


Chart 1.—Age distribution of mothers.

The surprising feature in the full term group is that 83 of the mothers had spontaneous deliveries, emphasizing the fact that the normal forces of labor may be, and often are, responsible for cerebral injuries. In some instances these injuries are not preventable. In some cases it is possible that an indicated forceps operation might have prevented injury; yet the patient finally had a spontaneous delivery.

In mothers having tumultuous labor or pituitary-like pains, anoxemia may be produced in the infant by the almost continuous systole of the uterus, not permitting fresh blood to the capillary bed of the placenta. In these cases pharmacologic analgesia or anesthesia may actually benefit the baby by decreasing the anoxemia and the actual force to which the infant is subjected.

*The Premature Group.*—In this group there were 25 cases of from six to seven months' gestation, 26 cases of from seven to eight months, and 4 cases of slightly more than eight months. Of this number, 46 were delivered spontaneously, 3 were delivered by low forceps, 4 were delivered by breech extraction and 2 were delivered by cesarean section. It was impossible to obtain accurate weights of the babies in the majority of the cases, but the smallest was apparently 1,280 Gm.

One of the cesarean sections in this group was done on a patient with eclampsia at eight months. The other section, as mentioned previously, was done after attempted induction had failed. Another mother with eclampsia was cared for at our University Maternity Hospital and delivered from below. The mothers of two infants had toxemias of late pregnancy and were delivered at seven and one-half and eight months.

Five children in this group were of twin births. The first was the second of twins born at seven months. The second was the first of twins delivered at seven and one-half months. The third was one of twins delivered at seven months, the other twin living but one day. Infant 4 was the second of twins delivered by cesarean section, while the fifth was a first twin, delivered by forceps.

As prematurity is a predisposing factor in cerebral spastic paralysis, any complication of pregnancy causing or necessitating premature labor is indirectly responsible. Toxemia, multiple pregnancy, placenta praevia or abruptio placentae may be listed as indirect factors. The latter two complications may be direct factors because of the producton of anoxemia.[3]

The proper conduct of the premature labor is imperative in the prevention of cerebral injury. Prevention of premature labor is of even greater importance. Of the 46 spontaneously delivered mothers in this group, none had episiotomies. We believe it is of more importance for the primipara in premature labor to have an episiotomy than it is for the primipara at full term. Certainly the head of an infant about to be born prematurely should not be permitted to pound against the perineum for more than one hour. It is much better, when there is any appreciable delay, that episiotomy be done and the mother be delivered by the low forceps method, if a perfect application can be made. The choice of analgesia in premature labors is also of much importance.

In our premature group, 39 mothers were primiparas. Of these, 2 had breech deliveries, 2 had low forceps deliveries and the remaining 33 were delivered spontaneously without episiotomy. Of the remainder of the 14 mothers, all had normal deliveries except 2 who had breech presentations. Of these babies there were 4 second born, 2 fourth born, 1 fifth born, 1 seventh born and 2 eighth born.

*The Use of Solution of Posterior Pituitary.*—Unfortunately, solution of posterior pituitary is too widely used for induction and augmentation of labor, in spite of continuous warning from teachers of obstetrics. In 12 mothers of this series, it was used in an attempt to induce labor. In 12 additional cases, it was given during labor. One infant, who was the sixth baby of her mother, was delivered after induction by solution

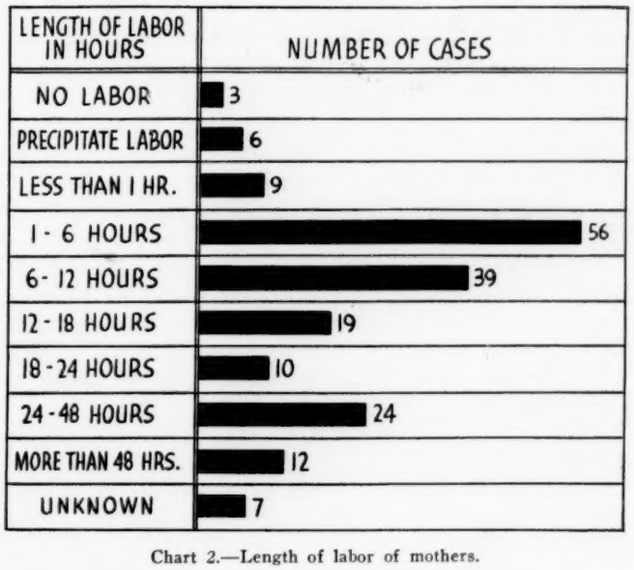


Chart 2.—Length of labor of mothers.

of posterior pituitary. The mother gave a history of each labor's having been induced by solution of posterior pituitary.

Regarding another mother given solution of posterior pituitary during labor, the physician stated that he wanted the baby to be born without instruments. In a third instance, a hypodermic injection was given ten

3. Clifford, Stewart H.: Asphyxia of the Fetus and the Newborn Infant, Am. J. Obst. & Gynec. **39**: 388-399 (March) 1940.

minutes before the birth of the baby. After the injection there was a continuous pain until the baby was born.

The fact that mothers of 24 out of 185 infants received solution of posterior pituitary either given to induce labor or given in labor before birth of the baby speaks for itself. In 13 per cent of our total number of cases solution of posterior pituitary had been used and was at least in part responsible for the resulting cerebral spastic paralysis.

*The Association of Apnea with Cerebral Injury.*—Attention has recently been called to the fact that apnea is associated with cerebral injury in the majority of cases of the latter. The employment of measures of resuscitation would certainly be positive evidence of apnea; however, many obstetricians routinely use the tracheal catheter to clear the airway of the newborn, so that this does not necessarily mean apnea. In this series of cases, the tracheal catheter was seldom if ever used. Obsolete methods of resuscitation such as spanking and immersion in hot and cold water were the methods chiefly employed. Of the 125 cases at or past term, resuscitation was employed definitely in 52 and was not employed in 69 instances. The remainder were

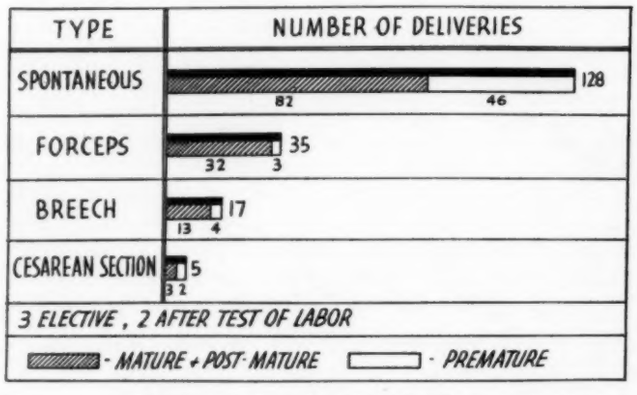


Chart 3.—Type of delivery of mothers.

questionable. The fact that resuscitation was not necessary in at least half of the cases is startling. Cyanosis was absent in 74 of these cases and present in 51. Convulsions occurred in 27 of the mature group and in 5 of the premature group.

In the premature group of 55 cases, resuscitation was not necessary in 33 cases and was necessary in 14 cases, the remainder being doubtful. Cyanosis was absent in 25 cases and present in 22 cases. Therefore, cerebral injuries many times exist in the absence of apnea or asphyxia.

*Preceding and Subsequent Pregnancies.*—In 2 mothers, both secundiparas, the first babies had been born by cesarean section, while their spastic children were second born and normal deliveries. The second of these also had three subsequent normal deliveries with normal babies.

No mother in the series has a second living spastic child though 1 patient, a tertipara in the group, had a subsequent breech delivery with a spastic child who died at six months. Her two preceding children had been normal.

One hundred and twenty of the mothers, including 67 of the primiparas, had no pregnancy after the birth of the spastic child. Fifty-two of the mothers had subsequent normal deliveries with normal babies; 3 others gave a history of difficult subsequent deliveries with normal babies and 3 had subsequent cesarean sections, 1 of the infants being stillborn.

## SUMMARY AND CONCLUSIONS

One hundred and eighty-five cases of cerebral spastic paralysis have been studied. Anesthesia and analgesia played little, if any, part in this series. There was an increased tendency to cerebral injury in infants of mothers having less than twelve hours of labor. The greatest number of cases was found in women having normal spontaneous deliveries, while 5 cases followed cesarean section. Thirty per cent of the babies were premature. The role of solution of posterior pituitary in contributing to the incidence of spastic paralysis was studied, as it was used in 13 per cent of the series. Cerebral spastic paralysis was present in many infants showing no clinical evidence of apnea or asphyxia.

1. The proper management of labor constitutes the best prevention of cerebral spastic paralysis.

2. Prevention and treatment of premature labor is the greatest single factor in the prevention of cerebral injury.

3. Solution of posterior pituitary continues to contribute to the incidence of cerebral spastic paralysis.

4. Cerebral injury in the newborn is not always preceded by asphyxia, as shown by the fact that at least half of the cases in this series were not associated with asphyxia.

5. It is our opinion that cerebral spastic paralysis may occur in many cases when labor has been faultlessly managed.

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## ABSTRACT OF DISCUSSION

DR. WARD F. SEELEY, Detroit: For about one hundred years a causal relationship has been known to exist between cerebral spasticity and birth injury. Many observers have reported a high incidence of asphyxia at birth in these cases. More recently the role of cerebral anoxia has been emphasized in the production of degenerative cerebral lesions with clinical manifestations of spasticity, convulsions or mental deficiency. Apnea is merely a clinical accompaniment in some of the cases in which cerebral anoxia may be present at birth. In the same category as asphyxia livida and asphyxia pallida, there is also an asphyxia occulta in which the brain may be wrecked even though there is no evidence of apnea. The fact that resuscitation was not necessary in at least half of the cases in this series should not be "startling" if the thesis of cerebral anoxia is accepted as the etiologic factor in the production of these lesions. External pressure on the fetal head or intracranial pressure from a subdural hematoma may shut off the local cerebral blood supply, causing a stagnant anoxia with cell destruction but without evidence of apnea at birth. Anoxic anoxia secondary to a premature separation of the placenta may have ruined the fetal cerebral cortex without visible birth apnea. Most important from the standpoint of the obstetrician is the histotoxic anoxic effect of analgesia, and analgesia which may be superimposed on already existing anoxic factors. I should like to know what type of anesthesia was used in the five cesarean cases—whether local, spinal or general. If the latter, a cerebral anoxia must be considered as having caused the cerebral degenerative changes since, as both Schreiber and Cole have intimated, asphyxia and cerebral degeneration are more apt to occur with general than with local or spinal anesthesia. The greatest danger to which the premature infant is exposed is a failure of the respiratory mechanism. If other anoxic hazards are added in the form of intervention, anesthesia or analgesia, and a spastic child results, the whole responsibility cannot be placed on the factor of prematurity, entirely ignoring any optional adjuvants. The authors

conclude that cerebral injury in the newborn is not always preceded by asphyxia, but it must be remembered that serious and sometimes preventable cerebral anoxia may be present without any clinical signs of asphyxia at birth.

DR. GERALD W. GUSTAFSON, Indianapolis: As 87.6 per cent of these patients were delivered in the home with a very small amount of analgesia, we have not considered analgesia to be a great factor in this particular series of cases. The second question is the type of anesthesia that was used in these cesarean sections. Few of the latter were done in Indianapolis, the majority being done in smaller communities throughout the state, and I am sure that the majority of the sections were done under ether anesthesia.

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# THE USE OF HISTAMINE IN THE TREATMENT OF SPECIFIC TYPES OF HEADACHES

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ROCHESTER, MINN.

Headache is undoubtedly among the most frequent ills to which the human flesh is heir. It is a complaint which has been known to mankind since the dawn of antiquity. Few contributions, however, have marked medical progress in this field.

It is not my purpose to review or consider the differential diagnostic features of the various types of headaches and head pains which have been recorded in the literature but rather to describe a new syndrome of vascular headache and to report the results of treatment with histamine. Other less well defined types of headaches have also been treated with histamine and the results will be reported.

This new syndrome of vascular headache, which MacLean, Craig and I [1] tentatively called "erythromelalgia of the head" and which I shall call "histaminic cephalgia" hereafter, was first encountered and recognized at the Mayo Clinic in September 1937. At that time the syndrome had not been described adequately in the literature. The observations which have been made with reference to this specific type of headache warrant its establishment as a distinct clinical entity, classic in its symptomatology and unique in its response to histamine therapy.

Since September 1937, 184 patients with a primary complaint of headache have been treated with histamine. Diagnoses of their condition ran the gamut of the nomenclature of headaches from psychoneurosis to organic lesions. Among these 184 patients were 72 with histaminic cephalgia. The first part of this paper will be confined to consideration of the 72 cases in which most of the classic features of this new syndrome of vascular headache were encountered. The second part will deal with the 112 cases of less well defined types of headache. Of the 72 patients with typical histaminic cephalgia, 45 were men and 27 women; ages ranged from 21 to 76 years. The majority were in the fourth and fifth decades of life. Symptoms had been present for from two months to thirty-five years. Before the cases are reported, however, the clinical picture of histaminic cephalgia must be defined if valid conclusions are to be drawn. The clinical picture was secured, not from published literature, for little is available, but from actual observations and complaints of patients.

From the Division of Medicine, the Mayo Clinic.

Because of lack of space, this article has been abbreviated in THE JOURNAL. The complete article appears in the author's reprints.

Read before the Section on Practice of Medicine at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Horton, B. T.; MacLean, A. R., and Craig, W. McK.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**: 257-260 (April 26) 1939.

## HISTAMINIC CEPHALGIA—THE CLINICAL PICTURE

Histaminic cephalgia is characterized by a unilateral headache, which usually begins in the later decades of life, is of short duration as it generally lasts less than an hour, commences and often terminates suddenly, tends to awaken the patient at night one to two hours after he has gone to sleep and is frequently eased by the patient sitting up or by standing erect. It is associated with profuse watering and congestion of the eye, rhinorrhea or stuffiness of the nostril, increased surface temperature and, often, swelling of the temporal vessels of the involved side of the head (fig. 1 *a* and *b*).

Pain is the outstanding complaint. It is constant, excruciating, burning and boring; it involves the eye, the temple, the neck and often the face. So severe and frequent are the attacks of pain (as often as twenty times a week) that practically every patient had contemplated suicide. The pain is not confined to the distribution of any cranial nerve but has a tendency to conform to the ramifications of the external carotid artery. During and following the attacks, marked tenderness is usually found when pressure is applied over the branches of the external and common carotid arteries. In the first stages of an attack, compression of the common carotid artery and sometimes the temporal artery frequently gives prompt relief. A few patients have discovered for themselves that compression of the artery on the side of the pain gives relief.

Parry [2] first made the discovery and described it fully in 1789.

The pain in all but 3 of the 72 cases of histaminic cephalgia was confined to one side of the head; in 2 of these 3 the whole head was involved, in the other only the occipital region. In 2 of these 3 cases lacrimation of both eyes occurred during attacks. The right and left sides of the heads of patients of both sexes were involved to about the same extent. Attacks were not accompanied by gastrointestinal symptoms or visual disturbances. Some of the patients had had migraine but the majority stated that they did not have periodic headaches in their earlier years. There was no relationship between the menstrual cycle and the bouts of pain. Fifteen of the patients had submitted to various operative procedures for relief of their pain before they came to the clinic. Most of them had had multiple operations. They were disabled by the disorder and had found no relief from the usual methods of treatment.

*Alcohol and Headaches.*—The use of alcoholic beverages precipitated attacks in 28 cases. When this effect had been noticed, patients had become total abstainers, but this did not result in cure. The use of beer, in a few instances, had precipitated attacks. During periods of spontaneous remissions, the use of alcohol would not cause attacks. References have been noted in the early literature regarding the relationship of the taking of alcohol to the production of headache.[3]

*Night Pain.*—In many instances the pain occurred with clocklike regularity, particularly at night. Thirty-one of the 72 patients had attacks of pain only at night.

2. Parry, C. H.: On the Effects of Compression of the Arteries in Various Diseases, and Particularly in Those of the Head, with Hints Towards a New Mode of Treating Nervous Disorders, Mem. M. Soc. London **3**: 77-113, 1792; also Edinburgh M. J. **25**: 366, 1826.

3. Liveing, Edward: On Megrim and Sick-Headache, London, J. & A. Churchill, Ltd., 1873. Parry.[2]

Patients would awaken out of a sound sleep with excruciating pain, night after night and week after week, at a certain hour; they would jump out of bed promptly in order to assume an upright position because, during the bout of pain, the reclining position was intolerable. Many patients had slept propped up on pillows and in rocking chairs for a number of weeks and even months prior to coming to the clinic because they had found that by this means the occurrence of the night pain could often be prevented. Although night pain was characteristic, pain during the waking hours was common. Remissions and exacerbations in many cases happened spontaneously. Most patients had had frequent attacks of pain for a year or more without a remission before coming to the clinic.

*Induced Attacks of Headache.*—In 35 of the 72 cases typical attacks of unilateral pain were induced by the subcutaneous injection of 0.1 to 1.2 mg. of histamine. In most of the other cases, no attempt was made to induce an attack. Patients were unable to distinguish between induced and spontaneous attacks, as the two seemed identical. When attacks were induced by the subcutaneous injection of histamine and the patients were under controlled environmental conditions, it was invariably demonstrated by means of electric thermocouples that, as the attack came on, the surface temperature of the involved side of the head rose more rapidly and to a higher level than that of the corresponding side of the head. It was never possible to induce attacks of this character by giving histamine to normal persons.

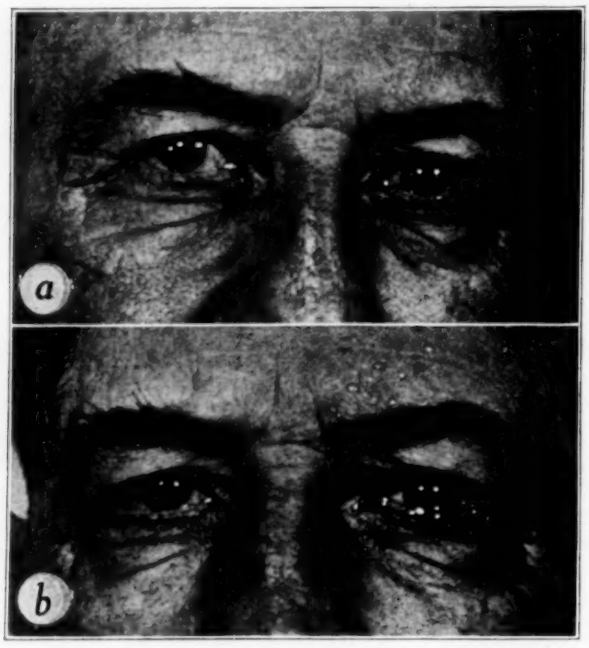


Fig. 1.—Appearance of a man aged 51 (*a*) before onset of attack and (*b*) during ten minute spontaneous attack of left "histaminic cephalgia." Watering of the left eye with increased perspiration above the left eyebrow is evident. Attacks had occurred three or four times a week for twenty-five consecutive years. Alcohol precipitated attacks; they could be induced by histamine.

When epinephrine (1:400,000 solution) was given intravenously to 5 patients who had either induced or spontaneous attacks, relief from pain was prompt. As the blood pressure rose from the resulting vasoconstriction, the pain disappeared. Placing the hand in ice water also immediately stopped the attacks of 4 additional patients. These 4 patients were hyperreactors to the cold pressor test,[4] and relief was the result of rise in blood pressure from reflex vasoconstriction. These observations seem to indicate that the head pain is on a vasodilating basis.

## REPORT OF TYPICAL CASES OF HISTAMINIC CEPHALGIA

CASE 1.—*History.*—A woman aged 37 registered at the clinic Sept. 7, 1937, complaining of attacks of severe pain on the right side of the head and face. These episodes came on with clocklike regularity at night and night after night had awakened her at the same time, usually between 3 and 4 a. m. The pain often persisted until 10 or 11 a. m., after which time she generally was free from distress. During attacks her right eye watered and was congested, and there was stoppage of the right nostril. The taking of alcohol precipitated earlier attacks. The pain was made worse by stooping over. There was a sensation of throbbing in the involved region, but trigger zones were never present. The first episode of this character had occurred in 1920 and lasted for two weeks. Later episodes appeared in 1929 and in 1934. Nausea, vomiting and scotomas were never present. She had taken as many as 24 tablets of 5 grains (0.3 Gm.) each of acetylsalicylic acid in one night without relief. The application of ice packs to the right side of the head during attacks had given partial relief, and the intravenous administration of 0.2 to 0.3 mg. of ergotamine tartrate (gynergen) had relieved her. Physical and neurologic examinations revealed nothing significant except considerable tenderness over the right carotid and temporal vessels as well as tenderness over the upper part of the neck. This tenderness was especially noticeable immediately after attacks. The blood pressure measured in millimeters of mercury was 115 systolic and 70 diastolic. The blood counts were normal and the serologic test for syphilis gave negative results. Roentgenograms of the thorax, skull and sinuses revealed negative results.

*Special Studies.*—The patient was observed during a spontaneous attack under controlled environmental conditions. The temperature of the room was 78 F. and the humidity was 40 per cent; the surface temperature of the patient's right temporal region was 34.4 C. (93.9 F.) at the height of the attack, whereas the surface temperature of the corresponding left temporal region was 33 C. (91.4 F.). Over the right zygoma the surface temperature was 34 C. (93.2 F.), and over the left zygoma 32.8 C. (91 F.). Ten minims (0.61 cc.) of epinephrine (1:1,000 solution), given subcutaneously, produced prompt relief.

Under the same controlled environmental conditions when the patient was without pain, the surface temperature of her right temple was 32.5 C. (90.5 F.) and of the left temple 31.5 C. (88.7 F.). One ounce (30 cc.) of alcohol was given by mouth. Forty-five minutes later the surface temperature of the right temple had increased to 34.3 C. (93.7 F.) and the left temple to 32.5 C. (90.5 F.). At this point an attack of pain developed, similar in every respect to a spontaneous attack. Compression of the common carotid artery on the right side relieved the pain, but it promptly recurred when pressure was removed. Ten minims (0.61 cc.) of epinephrine (1:1,000 solution) given subcutaneously produced prompt relief. Attacks were induced and the pain was relieved many times in this manner. The third time epinephrine (1:200,000 solution) was given intravenously and relief from pain was even more immediate.

Subcutaneous injection of 0.5 mg. of histamine precipitated an attack. In order to study the various phenomena associated with the attacks, the same quantity was given on several days. Succeeding attacks seemed progressively less severe and more difficult to precipitate. The possibility of desensitization with histamine was thus suggested. The patient then was desensitized with 0.1 mg. of histamine subcutaneously twice a day for approximately three weeks. After the first five days of this treatment she was free from attacks. She reported on May 17, 1940, that she had not had an attack since she left the clinic. She had a recurrence of the pain in the right side of the head

4. Hines, E. A., Jr., and Brown, G. E.: A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as an Index of the Prehypertensive State, Ann. Int. Med. **7**: 209-217 (Aug.) 1933.

in August 1940. It followed the hypodermic injection of morphine for relief of abdominal cramps. She was again desensitized with histamine and was again free from headache on Sept. 22, 1940.

It was noted in this case that after several injections the histamine seemed to lose its power to reproduce the pain. It occurred to me that these two phenomena might be related and that the gradually increasing resistance to histamine might in some way alter the phenomena of vasodilatation intrinsically associated with the appearance of pain in the spontaneous headache. It was in this manner that the desensitization treatment of histamine for this type of headache had its origin.

CASE 2.—*History.*—A woman aged 32, who registered at the clinic March 15, 1939, complained chiefly with reference to headaches over the left frontal and temporal regions associated with swelling about the left eye, drainage from the nose and congestive features in the chest. They invariably came

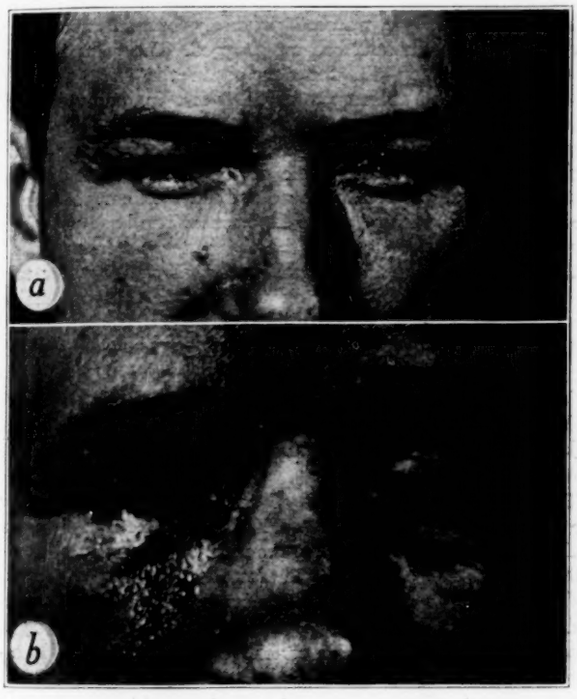


Fig. 2 (case 3).—Appearance of the eyes (*a*) before the onset of the attack and (*b*) during an attack induced with histamine. The swelling around the right eye and lacrimation of the right eye may be noted.

on at night and for two years she had slept in a chair or propped up in bed, as the erect posture tended to make the attacks less severe. Nausea, vomiting and scotomas had not been observed during severe attacks of pain. She had a sensation of increased heat in the left side of the head during an attack.

Routine physical examination and laboratory studies gave essentially negative results. Her blood pressure was 130 mm. systolic and 88 mm. diastolic.

*Special Studies.*—With the environmental conditions controlled as described in case 1, the patient was given 0.3 mg. of histamine acid phosphate subcutaneously. Rather marked flushing of the face, a choking sensation in the throat and throbbing in the left side of the face developed. Four minutes after injection of the histamine, pain developed in the left supraorbital region which she stated was of the same type as that which she had previously had at home except that it was milder. The pain increased in severity, both eyes began to water and the lids became swollen. The nose became congested and watered profusely. The surface temperature of the right temporal region increased 1.9 degrees C. (3.4 degrees F.), whereas that of the left temporal region increased 2.9 degrees C. (5.2 degrees F.). The induced attack persisted for approximately thirty minutes.

The patient was given 0.025 mg. of histamine subcutaneously twice daily; the dose was increased gradually, so that by the end of eight days she was receiving 0.1 mg. twice daily. This dosage was continued for three weeks. The attacks became less frequent and less severe after the first five days of treatment, and by the end of the ninth day the patient was entirely free from attacks and was able to sleep flat in bed without discomfort.

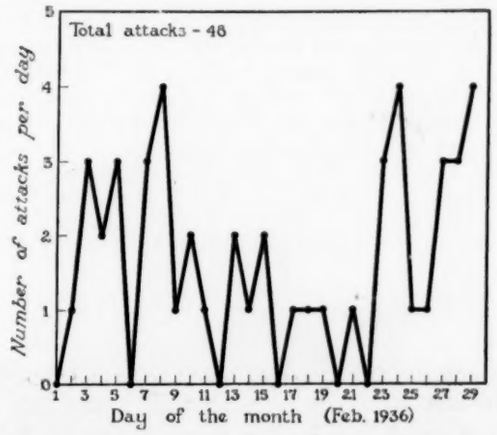


Fig. 3 (case 4).—Daily incidence of attacks of "histaminic cephalgia."

She had no additional treatment after leaving the clinic and remained well for three months. She then had a recurrence of pain on the left side. She again took a similar series of histamine injections twice daily for two weeks and was free from attacks for the next eight months. On recurrence of attacks which were identical to the original attacks, she was again desensitized with histamine and a maintenance dose of 0.1 mg. of histamine was given twice a week. The final report from her, dated May 10, 1940, stated that she was well.

CASE 3.—*History.*—A man aged 32, who registered at the clinic Aug. 14, 1939, complained chiefly at that time with reference to headaches which he had had for seventeen years. The average attack lasted for from thirty to fifty minutes. With the onset of pain, the right eye watered profusely but never became red.

*Special Studies.*—A typical attack of right hemicrania, in every way identical with his spontaneous pain, was produced by the subcutaneous injection of 1.1 mg. of histamine (fig. 2 *a* and *b*). This quantity was given in broken doses over a period of approximately twenty minutes, 0.2 to 0.3 mg. being given at each injection. The attack which was produced lasted fifty-five minutes.

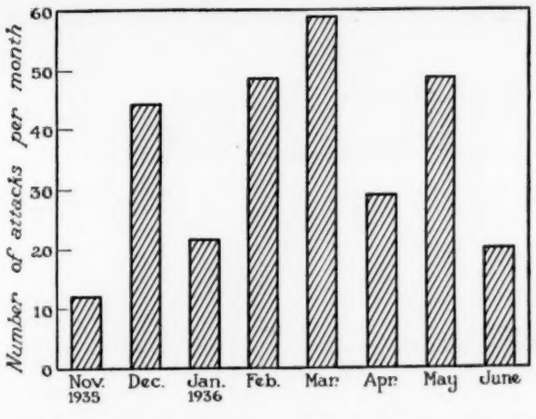


Fig. 4 (case 4).—The monthly incidence of attacks of "histaminic cephalgia" for eight months.

CASE 4.—A man aged 43, who registered at the clinic April 8, 1940, complained chiefly with reference to pain of the left side of the face, which localized around the left eye and the second division of the fifth nerve. Symptoms had begun in May 1934. Since that time he had had almost daily attacks except for

two periods of spontaneous relief from June 1938 to April 1939 and from June 1939 to March 8, 1940. The attacks, although they occurred throughout the entire year, tended to be worse in the spring. Shortly after his attacks had begun, he noted that a cocktail would precipitate the pain and, for that reason, he had refrained from the use of alcohol. During the two periods of spontaneous relief, he was able to take alcohol without any difficulty.

The average attack came on at night, usually one and a half hours after the patient had gone to bed, and was characterized by severe, excruciating pain in the left side of the face, and profuse watering of the left eye. In the severe attacks, drainage from the left side of the nose occurred. The attacks had all been alike but had varied in intensity. The average duration of the pain was from ten to fifteen minutes. He kept a diary of his attacks from October 1935 to June 1936 (figs. 3 and 4). He had three hundred and five attacks during this period. The largest number which occurred in a given day was six.

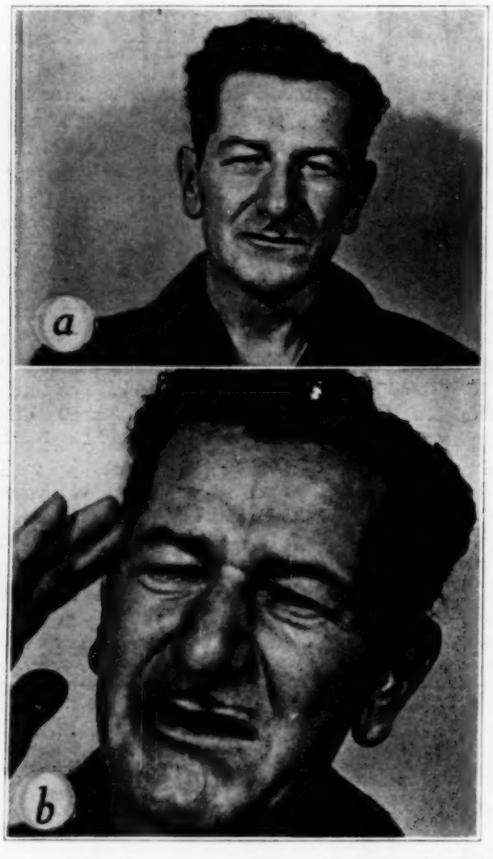


Fig. 5 (case 5).—Appearance of patient and eyes (*a*) before the onset of an attack and (*b*) during an induced attack of "histaminic cephalgia," in which the patient is pointing to the site of his pain, which was chiefly localized in the right temporal region.

The following special operative procedures had been carried out without benefit: In May 1935, 4 cc. of 88 per cent alcohol in solution of procaine hydrochloride had been injected into the second division of the left fifth nerve at its point of origin. Later in 1935 the left sphenopalatine ganglion had been injected with alcohol and procaine hydrochloride. In March 1936 the left cervicothoracic sympathetic nerves had been blocked by a paravertebral injection of procaine hydrochloride, but his attacks had become much more frequent and more severe. A general anesthetic had to be given for relief. In April 1936 an operation had been performed on the left sphenoid sinus without benefit. In June 1936 a window was made in the maxillary sinus on the left side, but this gave no relief from attacks.

When the patient was admitted to the clinic in 1940 his attacks were so frequent and so severe that he was sent to the hospital, where examination was carried out. Routine physical, laboratory and neurologic examinations revealed nothing significant. Shortly after he had had a spontaneous attack, the subcutaneous injection of 0.7 mg. of histamine failed to induce an attack. Twenty-four hours later, however, 1.0 mg. of histamine given subcutaneously produced an attack. Desensitization with histamine was started on April 13, and within a week he was entirely free from pain. He was dismissed from the clinic April 27, 1940, with instructions to take 0.1 mg. of histamine twice a week for an indefinite period. He reported on May 30, 1940, that he had remained entirely free from attacks, although he has been working harder than usual and again on Oct. 25, 1940, that he was perfectly well.

CASE 5.—*History.*—A patient had had his first attack of severe right hemicrania at the age of 14 years. It had come on at 2 a. m. and lasted for about half an hour. Since that time he had had a series of severe attacks each spring and each fall and occasionally in the summer. The average attack in 1939 when the patient was 36 years old lasted from one and a half to seven hours and almost invariably came on at night. The pain was only on the right side of the head. During attacks disturbance of vision and nausea or vomiting did not occur unless he swallowed a handful of pills in an attempt to get relief. The right eye watered profusely but did not become injected; the right nostril became plugged. The pain was much worse if lacrimation did not develop in the right eye. The pain was localized to a spot about 2 cm. in diameter in the right temporal region (figs. 5 and 6) but by 1939 it tended also to spread over the entire right side of the head distal to this region and down over the angle of the jaw. It was so severe that he frequently banged his head against the floor. He likened the pain to that which might be experienced if a hand were being slowly crushed in a vice. In the free intervals in a series of attacks, which lasted for several weeks, alcohol or beer taken by mouth promptly brought on the pain. During remissions, he could take alcohol without difficulty.

A change in environmental temperature often precipitated an attack. Morphine, when taken hypodermically, did not give relief. Acetylsalicylic acid, 20 grains (1.3 Gm.) gave more relief than any other drug. He had never been able to hold a job because the attacks occurred so frequently and were so severe.

The patient was 31 years of age when he first came to the Mayo Clinic, July 3, 1934. Physical and neurologic examination gave essentially negative results. The blood pressure was 120 mm. systolic and 80 mm. diastolic. Because the patient insisted, a right cervicothoracic sympathetic ganglionectomy and trunk resection was performed on July 12. Following this procedure, he had only mild attacks which lasted for fifteen or twenty minutes every month or so.

On each of the twenty-two days prior to his second admission, Sept. 2, 1936, however, he had had severe attacks which lasted for from four to six hours. These came on shortly after midnight. The severe paroxysms of pain made it imperative that something be done. Accordingly on Sept. 4, 1936, the middle meningeal artery was explored through a subtemporal craniotomy. It was found to be large and tortuous and to have a particularly large posterior branch. The artery was dissected free and ligated. Three days later encephalography gave negative results.

The patient's final admission to the clinic was Aug. 11, 1939. He had been having severe attacks daily and sometimes three or four a day during the previous three weeks. A general examination at this time gave negative results and the neurologic examination indicated only the presence of a right Horner's syndrome.

After attacks ceased, the skin over the right temporal region was extremely tender. The patient preferred to sit up rather than lie down during the day and night because posture seemed to be an important factor in precipitating the attack. However, sleeping in a semisitting position did not prevent the occurrence of attacks.

*Special Studies.*—A typical attack of right hemicrania was produced by the subcutaneous injection of 1 mg. of histamine (figs. 5 and 6). It was identical in every respect to the spon-

taneous attacks which were observed. The patient was unable to distinguish between the two. Pain was confined to the right side of the head.

Because of the frequent and severe occurrence of pain, histamine desensitization was started Aug. 14, 1939. Subcutaneous injections were given every six hours day and night. The initial dose was 0.01 mg., and the dosage was increased gradually up to 0.1 mg. by the end of seven days. His attacks after the first two days of this therapy became less frequent and less severe and disappeared by the ninth day. The final report from him, dated May 27, 1940, stated that he had not had an attack of pain since leaving the clinic.

### DIFFERENTIAL DIAGNOSIS

The syndrome of histaminic cephalgia need not be confused with that of classic migraine. Patients with histaminic cephalgia have frequent short attacks of pain which usually can be measured in terms of minutes or hours and which usually come on suddenly and disappear in a like manner. The attacks begin later in life and are not associated with nausea, vomiting or visual disturbances. There is no hereditary background for the occurrence of these attacks. On the other hand, patients with migraine have attacks of longer duration which almost invariably are accompanied by nausea, vomiting and visual disturbances. Furthermore, at least 85 to 90 per cent of persons with migraine state that one or more members of the family have had migraine. Histaminic cephalgia is not to be confused with trigeminal neuralgia because trigger zones which are found invariably in the presence of trigeminal neuralgia are absent. The pain in trigeminal neuralgia follows the distribution of the first, second or third division of this nerve, whereas the distribution of the pain in histaminic cephalgia is not confined to the anatomic distribution of any cranial nerve but seems to correspond more or less to the anatomic ramifications of the external carotid artery.

### TREATMENT

The object of treatment is, first, to free the patient from pain, which usually can be accomplished without any great difficulty; second, to determine the proper maintenance dosage. Histamine diphosphate is the drug employed. To attain the first of the foregoing objectives, a "desensitization" program is inaugurated.

The term "desensitization" is used here in the broadest sense. No specific allergic or hypersensitive states have been definitely demonstrated to be related to the symptoms of the patients. The prolonged favorable effect of repeated small doses of histamine in these cases suggests that the action of the drug is in the nature of a desensitization.

Treatment is given according to the following schedule: The contents of a 1 cc. ampule of histamine diphosphate (0.275 mg.) is equivalent to 0.1 mg. of histamine base. Ampules of this character are now on the market. (All doses are given subcutaneously.) The quantity given at each injection is as follows: first injection, 0.25 cc.; second, 0.30 cc.; third, 0.35 cc.; fourth, 0.40 cc.; fifth, 0.45 cc.; sixth, 0.50 cc.; seventh, 0.55 cc.; eighth, 0.60 cc.; ninth, 0.65 cc.; tenth, 0.70 cc.; eleventh, 0.75 cc.; twelfth, 0.80 cc.; thirteenth, 0.85 cc.; fourteenth, 0.90 cc.; fifteenth, 0.95 cc.; sixteenth, 1.00 cc.; seventeenth, 1.00 cc.; eighteenth, 1.00 cc.; nineteenth, 1.00 cc.; twentieth, 1.00 cc.

If, at any time, the patient notices slight flushing of the face or any other symptoms indicating subjective or objective response to the drug, the next dose should be reduced 50 per cent. An attempt then is made gradually to increase the dose again.

These increasing subcutaneous injections are administered twice daily for approximately ten days to three weeks. After the patient is free from attacks, the second phase of the problem is to prevent future attacks. This can best be accomplished by giving each patient a proper maintenance dosage. This will consist in giving the patient approximately 1 cc. of histamine diphosphate (0.275 mg. of histamine diphosphate) one to three times weekly. The average patient will probably require two injections weekly, whereas a few patients apparently do not require a maintenance dose. I have had many letters of complaint from physicians telling me of their difficulties, and invariably these difficulties have arisen because the patient had been given an overdose of the drug. Injections must be given subcutaneously, not intracutaneously or intravenously. It is easier to give the drug correctly than incorrectly.

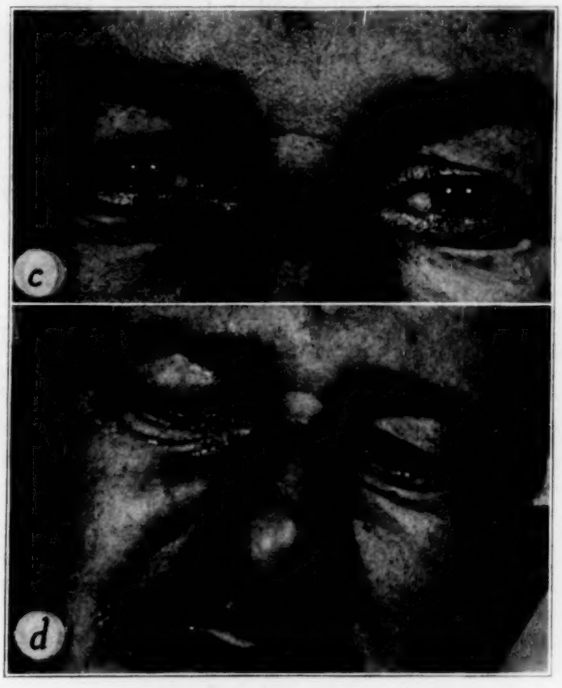


Fig. 6 (case 5).—Close-up of patient: *c*, before the onset of an attack; *d*, lacrimation of the right eye with tears flowing down the right cheek and slightly increased perspiration above the right eye.

### RESULTS OF TREATMENT OF HISTAMINIC CEPHALGIA

*Histamine.*—The 63 patients with histaminic cephalgia who were desensitized with histamine will be considered in two groups. Fifty-one of the 63 patients had all the signs and symptoms of typical histaminic cephalgia, whereas 12 had some atypical features. For that reason the results will be reported separately. In 48 of the 51 typical cases, complete relief of symptoms was obtained for varying periods after desensitization. Concerning 3 of these patients, follow-up information is not available. Information received less than a month before June 1, 1940 indicated that 27 patients considered themselves perfectly well. Three additional patients were perfectly well when they were last heard from, approximately sixteen months earlier. Eighteen were still having headaches, but their attacks were much less frequent and much less severe than formerly. Five of the patients who were perfectly well had had no treat-

ment since they left the clinic. The longest period which had elapsed without treatment being given was thirty-three months. Ten of the 27 patients who considered themselves perfectly well were receiving a maintenance dose of 0.1 mg. of histamine either once or twice weekly.

Of the 12 patients who had somewhat atypical signs and symptoms of histaminic cephalgia, 4 were relieved completely of their symptoms at the time of dismissal from the clinic and remained well for periods varying from one month to nine months. One patient was still free from attacks at her last report May 10, 1940, or about two months after dismissal. She had typical histaminic cephalgia except that the pain was located in the occipital region. The other patients in this group obtained from 50 to 90 per cent relief of pain immediately after completion of treatment but had recurrences, which most stated were less frequent and less severe than their former attacks.

*Histaminase.*—Because such excellent results had been obtained from the use of histamine in this group of headaches, it was decided to treat 9 patients with typical histaminic cephalgia with histaminase by mouth. Typical attacks were reproduced by the giving of histamine subcutaneously in 3 subjects. These 9 patients were all having from one to three attacks each twenty-four hours and had had to stop work because of their frequent bouts of pain. Eight obtained excellent results from the use of this drug. The longest period without recurrence to June 1, 1940 was ten months; the shortest, one month.

*Results of Treatment of Various Types of Headache with Histamine*

| | | | No Relief | | Less Than 50 per Cent Relief | | More Than 50 per Cent Relief | |
|---|---|---|---|---|---|---|---|---|
| Group | Cases | Hemicrania | Cases | Per Cent | Cases | Per Cent | Cases | Per Cent |
| 1 | 44 | 44 | 20 | 45.5 | 12 | 27.3 | 12 | 27.3 |
| 2 | 36 | 9 | 17 | 47.2 | 10 | 27.8 | 9 | 25.0 |
| 3 | 13 | 8 | 6 | 46.2 | 6 | 46.2 | 1 | 7.7 |
| 4 | 19 | .. | 9 | 47.4 | 5 | 26.3 | 5 | 26.3 |
| Total | 112 | | 52 | 46.4 | 33 | 29.5 | 27 | 24.1 |

## HISTAMINE TREATMENT OF OTHER TYPES OF HEADACHE

As previously stated, 184 patients with a primary complaint of headache have been treated with histamine. Among these were 112 whose headaches had none of the features of histaminic cephalgia. The only common features of the headaches of the patients constituting this group of 112 cases were the long duration of symptoms, resistance to ordinary forms of treatment, the willingness on the part of the patients to devote two or three weeks to treatment and the disabling intensity of symptoms. Many of the patients were unable to work because of frequent and severe headaches. They remained for treatment because they insisted that something be done to relieve them of their attacks. An analysis of the clinical types within this group of 112 cases and their response to therapy leads to some well defined conclusions.

All of these patients received subcutaneous injections of histamine (0.05 to 0.1 mg.) twice daily. The usual course consisted of thirty to fifty injections, although some patients received more than one course. Eighty-two of these patients received no other treatment. The remaining 30 received, in addition, histamine intravenously or histaminase orally. In all cases, however, the subcutaneous desensitization with histamine was the basic therapy. Fifty-three of these patients were observed at intervals or reported by letter for more than six months, and 72 for more than three months. Most of those patients who did report or return for observation within three months did not receive any relief even temporarily; this made further observation unnecessary for evaluation of therapy. A few patients who received moderate relief were not under observation or heard from for more than two months.

Three arbitrary categories of improvement were established for the sake of this study. These are as follows: (1) no improvement; (2) less than 50 per cent relief; in this group are included cases in which relief was not known to have lasted more than two months; and (3) more than 50 per cent relief; in this category are included a few in which complete relief lasted for as long as a year. The cases were divided, on clinical grounds into four groups. Grouping criteria were broad and arbitrary, as follows:

In group 1 were included the cases of hemicrania with the prominent features of migraine. Two or more of the following features were present in each case: (1) attacks associated with vomiting, of consistent nature and duration; (2) prodromes or scotomas; (3) hemicrania among at least 2 other members of the family; (4) duration of the typical attack for thirty-six hours or more, and (5) complete freedom from pain at intervals. Cases of apparent psychic predisposition were not included in this group. In group 2 were the cases of headache with prominent psychogenic features. In group 3 the headache was associated with known cephalic organic disease. Cases of such conditions as brain tumor, latent cerebrospinal syphilis, cerebral cortical atrophy, marked hypertension and those in which multiple operative procedures had been performed were included. In group 4 were the miscellaneous cases. In some cases clinical details were inadequate or too confused to classify otherwise, but in this group were included 5 cases in which the pain consistently was localized to a very small region, such as one eyeball. The results of treatment in these groups of cases are given in the accompanying table.

The trend of improvement in each clinical group closely followed that shown in the sample as a whole. In view of the diverse characteristics of the clinical conditions typified by these groups, this observation suggests either that histamine therapy had uniformly beneficial effects on each type, which is hardly credible, or that it had no effect on any group included in this total sample. Lacking a control group of untreated or placebo treated patients, the spontaneous remission rate is conjectural, but at all events the improvement noted does not exceed a reasonable expectation of spontaneous relief, especially as it is likely that most patients consulted the clinic at the peak of their symptoms.

In the psychogenic group (group 2) a greater or more prolonged incidence of relief than that of the other groups was not noted. This implies that, as administered at the clinic, histamine is not an effective psychotherapeutic or suggestive measure. From this critical study histamine therapy does not appear to be particularly effective in treatment of the commoner types of severe headache, although the majority of the subjects felt that they obtained temporary benefit.

## SUMMARY AND CONCLUSIONS

Seventy-two cases illustrate a new syndrome, "histaminic cephalgia," associated with clinical and laboratory evidence of vasodilatation. This type of headache represents a distinct clinical entity which is unique in its symptomatology and its response to histamine therapy. Attacks can be induced at will with given amounts of histamine and can be eradicated by desensitization with histamine. A maintenance dose of 0.1 mg. of histamine twice weekly is usually necessary to prevent recurrence of attacks. The spectacular manner in which patients respond indicates that histamine treatment is as specific for this syndrome as insulin is in the treatment of diabetes mellitus. The observations which have been made at the clinic since September 1937 and the results which have been obtained by means of histamine therapy justify this conclusion. Surgical intervention for the relief of this type of pain seems to be unwarranted. Histamine therapy is not effective in treatment of commoner types of severe headache.

For purpose of classification, the term "histaminic cephalgia" is suggested as descriptive of the entity with which we have been dealing. This term seems logical in view of the fact that patients are unable to distinguish between attacks induced with histamine and spontaneous attacks. Furthermore, the disease can be promptly eradicated by desensitization with histamine.

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## ABSTRACT OF DISCUSSION

DR. EMANUEL LIBMAN, New York: Dr. Horton has presented an original piece of work in an admirable way. He has made a beginning in sifting out the cases of "migraine." As one looks up what the best writers have said, one will find a great deal of confusion. Even headaches evidently due to sinusitis have been included. The syndrome described by Dr. Horton differs from migraine. It comes on at a much later period of life and many of the typical phenomena of migraine are missing. I would not lay too much stress on the influence of alcohol, because it has a tendency to increase a number of varieties of headaches, especially the headache due to sinusitis. Flushing has been described in migraine. Oppenheim noted it in "vasomotor cephalalgia," a condition which may be associated with urticaria. This flushing is not accompanied by lacrimation. In headaches due to sinusitis one can have lacrimation, but it is usually not as marked or it does not come on as acutely and disappear as abruptly. Headaches due to sinusitis may be periodic and may occur only late at night, but under such conditions fever and other toxic phenomena are usually present. It would be of interest to learn the origin of the intoxication in the cases described by Dr. Horton. Has any relationship to the carotid sinus been noted? Dr. Horton has found histamine of value in Ménierè's disease. As a result of the varied investigations he is carrying out on the therapeutic value of histamine, we may expect him to provide us with other valuable leads. This and other contributions that Dr. Horton has made show that a wide field remains for purely clinical research. Often young men are told that there are now no fruitful fields in clinical medicine and pathology. This is wrong. There are many avenues of progress open in these disciplines. As biochemistry, experimental physiology and related subjects advance, changes must be made in our clinical classification and in our concepts of pathologic changes. If the experimental work with histamine had not been done, Dr. Horton could not have segregated his syndrome. While we all realize the continually increasing importance of animal experimentation, we must be careful not to stress the need of animal experimentation when clinical studies alone may suffice or give results not obtainable by animal experimentation.

DR. LEONARD G. ROWNTREE, Philadelphia: I think we are listening to medical history in the making. Dr. Horton has recognized a new disease, he has defined it, named it, determined its pathogenesis, reproduced it in subjects at will and has devised a cure for it. I have never heard of any device, recognized and introduced so handily, where one man, with deepness, quickness and dispatch, has handled the whole situation personally, and this marks Dr. Horton as a clinician of distinction. This disease is a syndrome which may be defined as a regularly recurring, severe and often excruciating paroxysmal unilateral headache of brief duration, affecting during the night middle aged and elderly persons and awakening them from their sleep. The pain conforms to the distribution of the external carotid artery and is due to vasodilatation secondary to the release of histamine and can be produced at will in the subjects of this disease. The attacks are accompanied by signs of congestion in the area involved, lacrimation, rhinorrhea, the subjective feeling of heat locally, actual increase of temperature as determined by the thermometer, and swelling of the temporal arteries. These attacks are as distinct as migraine or as tic douloureux, and they are related to neither. It represents a histamine type of attack. It is reproduced by histamine. It is brought out through desensitization, and it is controlled by histaminase. I believe he is right, that histamine is a specific, as insulin is in diabetes. Dr. Horton has been a student for many years of vascular disease, particularly peripheral vascular disease, and also of the drug histamine. This is the outgrowth of a natural flair for investigation and good training, careful study of patients, an abundant opportunity to study patients and, above everything else, intellectual thinking. I would like to ask if he can give us any idea as to the nature of the local mechanism, because there must be one, and what has come to pass when he has attempted this same experiment in cases in which the sympathetics to this region have been removed for other purposes.

DR. BAYARD T. HORTON, Rochester, Minn.: I have attempted to describe only what I have seen and what my patients have told me. Many of my colleagues, especially Dr. A. R. MacLean, have contributed much to the success of this work. The exact mechanism by which this syndrome of vascular headache is produced is not clear. Experimental and clinical data indicate a local release of histamine with resultant vasodilatation which is almost exclusively confined to the ramifications of the external carotid artery. During induced attacks, with patients under controlled environmental conditions, the surface temperature of the involved side of the head invariably rises more rapidly and to a higher level than that of the opposite side of the head. This obviously indicates local vasodilatation. A sensitive carotid sinus has not been noted in this series of patients, nor do I think that it has been responsible for the production of this particular type of headache. I have seen a few patients who had the pain but did not have definite lacrimation. Unilateral lacrimation is a prominent feature in the average case. Prior to coming to the clinic, two patients had undergone cervical sympathectomy for the purpose of eradicating the pain, but they received little or no benefit from this surgical procedure. Desensitization with histamine, however, did eradicate their attacks. Dr. Libman and Dr. Rowntree are right in suggesting that "erythromelalgia of the head" is not an appropriate term to use in describing this syndrome. We originally suggested the term "erythromelalgia of the head" as a descriptive term for this syndrome because of the vasodilating features. In doing so, we regarded the head as a fifth extremity. Dr. Rowntree suggested the term "erythrocephalalgia" which I think is better than the one we originally employed. Regardless of the terminology, I doubt whether any syndrome in clinical medicine is more spectacular or clear cut than that which I have attempted to describe. My observations certainly seem to warrant the establishment of this type of headache as a distinct clinical entity. The syndrome lends itself beautifully to experimental study. The attacks can be reproduced so accurately that patients are unable to distinguish between induced and spontaneous attacks. Furthermore, the syndrome can be eradicated promptly by desensitization with histamine. I cannot escape the conviction that the use of histamine in the treatment of this syndrome is as specific as insulin is in the treatment of diabetes mellitus.

# THE ROLE OF CHLORIDES IN ALKALOSIS

## FOLLOWING THE ADMINISTRATION OF CALCIUM CARBONATE

JOSEPH B. KIRSNER, M.D.
AND
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The term "alkalosis" was used originally by Fischler [1] in 1911 with reference to the toxemia of animals with Eck fistulas because the disturbance was attributed to a disproportion between the acid and base in the body. Alkalosis has since assumed increasing significance in relation to various experimental and clinical problems. It was first reported as a complication of the Sippy treatment of peptic ulcer by Grant [2] in 1922, although Sippy himself had previously recognized its occurrence.[3] Its manifestations have now become familiar to most clinicians as a result of the detailed accounts of Hardt and Rivers,[4] Ellis,[5] Gatewood and his associates [6] and others.[7] Despite the fact that the original Sippy powders were mixtures of sodium bicarbonate and calcium carbonate, the systemic effects of alkali administration were attributed entirely to the highly soluble sodium bicarbonate, and the influence of calcium carbonate on the electrolyte balance received only occasional consideration. It was assumed originally that this alkali had little or no effect on the acid-base balance and mineral metabolism.[8] A recent paper by McGee and others [9] likewise indicated that moderate amounts of calcium carbonate did not significantly alter the acid-base equilibrium. In contrast to these studies are the reports of Wildman,[10] Gatewood and his associates,[6] Cooke,[11] and Cope [12] describing the occurrence of alkalosis in patients receiving only calcium carbonate. In this report we present a further study of the alkalosis following the administration of calcium carbonate and refer particularly to the role of chlorides.

### METHOD OF STUDY

A series of 105 patients with peptic ulcer, including both sexes and of ages from 16 to 78, has been treated with large doses of calcium carbonate during the past three years. Alkalosis, as evidenced by a disturbance in the acid-base equilibrium, developed in 32 of these. The serum carbon dioxide combining power, $p_H$ and chlorides and the blood urea nitrogen were determined [13] at different periods during treatment, the number of such determinations varying with the individual case. The normal values for these procedures are carbon dioxide 22 to 30 millimols per liter, $p_H$ 7.35 to 7.45, chlorides 100 to 110 millimols per liter and blood urea nitrogen 9 to 15 mg. per hundred cubic centimeters. In addition to the routine examinations of urine, renal function was estimated by the urea clearance method of Van Slyke.[14] These values are expressed as the percentage of average normal after correction for individual surface area by the method of Peters and Van Slyke;[15] 75 per cent is generally accepted as the lower limit of normal. Although a normal urea clearance may not exclude the possible presence of renal disease,[16] it is considered one of the most reliable measures of renal function in use today.[17]

### CLINICAL ASPECTS

It is of interest to note that no direct correlation existed between the amount of calcium carbonate received and the development of alkalosis. The acid-base balance remained within normal limits in some cases after the ingestion of as much as 48 Gm. daily for forty-two days, while alkalosis occurred in other persons taking as little as 15 Gm. for four days.

The symptoms of alkalosis usually appeared between the third and eighth days of treatment, although in several instances not until after fourteen to eighteen days had elapsed. The significant complaints were a distaste for milk and cream, excessive dryness of the mouth and throat, anorexia, dizziness, headache, weakness, nausea and occasionally vomiting. Tetany, convulsions and coma were notably absent. Symptoms did not occur in several patients despite the presence of a severe chemical alkalosis. There was no consistent correlation between the severity of complaints and the degree of chemical alkalosis, an observation previously noted by Eisele.[18]

### ACID-BASE BALANCE

Alkalosis is characterized chemically by an elevation of the carbon dioxide combining power of the blood, a decrease in the hydrogen ion concentration (rise in $p_H$) and a fall in the serum chlorides. In this series (table 1) the serum carbon dioxide remained within normal limits in 73 patients. In 12 persons with moderate alkalosis the carbon dioxide varied between 31.7 and 37.0 millimols per liter. The serum carbon dioxide was considerably higher in the 20 patients with severe alkalosis, exceeding 40 millimols per liter in 10 cases and reaching a peak of 47.4 millimols per liter in one instance. The serum $p_H$ paralleled the carbon dioxide. Temporary values of 7.50 were occasionally observed in patients with an otherwise normal electrolyte balance. The $p_H$ during alkalosis varied between 7.50 and 7.73, exceeding 7.60 in 11 patients. The highest value

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Read before the Section on Pharmacology and Therapeutics at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Fischler, F.: Ueber die Fleischintoxikation bei Tieren mit Eck'scher Fistula, Der Krankheitsbegriff der Alkalosis, Deutsches Arch. f. klin. Med. **104:** 300, 1911.
2. Grant, S. B.: Tetany: A Report of Cases with Acid-Base Disturbance, Arch. Int. Med. **30:** 355 (Sept.) 1922.
3. Personal communication.
4. Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, Arch. Int. Med. **31:** 171 (Feb.) 1923.
5. Ellis, A. W. M.: Disturbance of the Acid-Base Equilibrium of the Blood to the Alkaline Side: Alkalemia, Quart. J. Med. **17:** 405 (July) 1924.
6. Gatewood, W. E.; Gaebler, O. H.; Muntwyler, Edward, and Myers, V. C.: Alkalosis in Patients with Peptic Ulcer, Arch. Int. Med. **42:** 79 (July) 1928.
7. Jordan, Sara M.: Calcium, Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, J. A. M. A. **87:** 1906 (Dec. 4) 1926. Oakley, W. M.: Alkalosis Arising in the Treatment of Peptic Ulcer, Lancet **2:** 187 (July 27) 1935. Cooke.[11] Berger and Binger.[30] Jeghers and Lerner.[31]
8. Lovenhart, A. S., and Crandall, L. A.: Calcium Carbonate in the Treatment of Gastric Hyperacidity Syndrome and in Gastric and Duodenal Ulcer, J. A. M. A. **88:** 1557 (May 14) 1927.
9. McGee, L. C.; Martin, J. E., Jr.; Levy, Fritz, and Purdum, R. B.: The Influence of Alkalis on Renal Function, Am. J. Digest. Dis. **6:** 186 (May) 1939.
10. Wildman, H. A.: Chloride Metabolism and Alkalosis in the Alkali Treatment of Peptic Ulcer, Arch. Int. Med. **43:** 615 (May) 1929.
11. Cooke, A. M.: Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcer, Quart. J. Med. **1:** 527 (Oct.) 1932.
12. Cope, C. L.: Base Changes in the Alkalosis Produced by the Treatment of Gastric Ulcer with Alkalis, Clin. Sc. **2:** 287 (July) 1936.
13. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, William & Wilkins Company, 1931, vol. 2: Serum Carbon Dioxide, p. 283; $p_H$ (Colorimetrically), p. 796; Chlorides, p. 835; Blood Urea in Nitrogen, p. 554.
14. Van Slyke, D. D., and others: Observations on Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy, Medicine **9:** 257 (Sept.) 1930.
15. Peters and Van Slyke: Quantitative Clinical Chemistry,[13] p. 568.
16. Alving, A. S., and Van Slyke, D. D.: The Significance of Concentration and Dilution Tests in Bright's Disease, J. Clin. Investigation **13:** 969 (Nov.) 1934. Van Slyke.[14]
17. Cope, C. L.: The Reliability of Clearance Tests for Renal Efficiency, Clin. Sc. **2:** 35 (Sept.) 1935.
18. Eisele C. W.: Changes in Acid-Base Balance During Alkali Treatment for Peptic Ulcer, Arch. Int. Med. **63:** 1048 (June) 1939.

obtained was 7.73. During the course of calcium carbonate therapy the serum chlorides ranged between 95 and 105 millimols per liter in the normal group. In general the chloride curves were mirror images of the carbon dioxide and $p_H$ curves. In moderate alkalosis the lowest chloride values varied between 81.0 and 96.4 millimols per liter and in 5 cases were below 90 millimols per liter. In severe alkalosis the lowest chloride values varied between 65.8 and 89.4 millimols per liter. In all these cases the chlorides were below 90, and in 5 patients the values were below 80 millimols per liter.

The total base [19] was determined in 20 patients, 12 with a normal acid-base balance and 8 with alkalosis. Contrary to the observations of Cope,[12] the values did not exceed the normal range of 150 to 160 milliequivalents per liter and there was no significant variation in the total base of patients with and without alkalosis. Kiefer,[20] among others, has also noted the occurrence of alkalosis without an appreciable rise in total base.

The serum calcium and phosphorus were determined in 23 patients with a normal electrolyte balance and in 5 patients with alkalosis. All values were normal except in 1 patient with pyloric stenosis in whom a serum calcium of 13.1 mg. was obtained. There was likewise no evidence to suggest that either anemia [21] or hepatic disease [22] played a significant role in the development of alkalosis.

### RENAL FUNCTION

Among the various theories which have been proposed to account for the development of alkalosis in patients receiving alkalis, greatest emphasis has been placed on antecedent renal disease as a major etiologic factor. Thus, Wilkinson and Jordan,[23] using the sulfate clearance test, noted preceding renal damage in a large number of patients in whom alkalosis later developed. The high incidence of alkalosis in persons with hypertension and nephritis has also been frequently reported in the literature.[24] Although this relationship is undoubtedly true in many cases, it does not explain alkalosis occurring in patients without evidence of renal disease,[25] the increase in tolerance to alkalis observed in some cases without improvement in renal function [20] or the absence of alkalosis during therapy in patients with definite renal disease.[7] Normal renal function was present in 22 of 32 cases in the present series before the development of alkalosis. Twelve patients with lowered renal efficiency showed no disturbance in the acid-base balance during treatment. It is interesting to note the absence of alkalosis in 3 patients with hypertension and in one person who had undergone a nephrectomy 26 years previously.

TABLE 1.—*Acid-Base Balance During Administration of Calcium Carbonate*

| | $CO_2$ (mM/L) | Cl (mM/L) | $p_H$ |
|---|---|---|---|
| No alkalosis ..... (73 patients) | 22-30 | 95-105 | 7.35-7.45 |
| Moderate alkalosis ..... (12 patients) | 31.7-37.0 | 81.0-96.4 | 7.50-7.60 |
| Severe alkalosis ..... (20 patients) | 35.0-47.4 | 65.8-89.4 | 7.50-7.73 |

TABLE 2.—*Effect of Sodium Chloride on Urea Clearance and Acid-Base Balance (Calcium Carbonate Continued—27 Patients)*

| | |
|---|---|
| Normal clearance at all times | 2 |
| Persistent lowering of clearance | 2 |
| Return to original clearance | 23 |
| Return to normal acid-base balance | 27 |

It has been reported [26] that during alkalosis the urine frequently contains albumin, casts and red blood cells. In our experience this is unusual. The blood urea nitrogen, however, may rise to high levels and fall with recovery.[27] The blood creatinine, inorganic phosphates and inorganic sulfates may do the same. Urea and sulfate clearances, as well as the excretion of phenolsulfonphthalein, have been found reduced by various workers.[28] The mechanism by which the decrease in renal function is brought about and the nature of the renal lesion have not been conclusively determined. McCance and Widdowson observed a decided improvement in the creatinine, urea, inulin, phosphate, sodium, ultrafiltrable calcium and magnesium clearances after recovery from alkalosis in a patient with pyloric stenosis. The improvement in the inulin clearance strongly suggested that the major dysfunction was a decrease in glomerular filtration.

In the present series, the urea clearance during alkalosis decreased in 25 of the 32 patients. In 9 cases the clearance dropped to levels as low as 12, 13, 15, 17, 17, 17, 18.5, 20 and 22 per cent of average normal. The blood urea nitrogen rose concomitantly, reaching a peak of 67.6 mg. per hundred cubic centimeters in 1 patient. The urine in 2 patients contained traces of albumin. In a third case, acid urine containing albumin, casts and red blood cells was secreted at the height of the alkalosis. This was the only instance, in this series, of acid urine during alkalosis. The secretion of acid urine under these circumstances has been reported frequently,[29] however, and indicates the presence of severe renal damage. The urea clearance remained unchanged in 7 patients, although in 3 the alkalosis was pronounced. Normal clearance values had been obtained previously

19. Stadie, W. C., and Ross, E. C.: Micro Method for Determination of Base in Blood and Serum and Other Biological Materials, J. Biol. Chem. **45**: 735 (Oct.) 1925.

20. Kiefer, E. D.: The Interdependence of Gastric Secretion and the $CO_2$ Content of the Blood and Its Significance in the Alkali Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **4**: 667 (Dec.) 1937.

21. Hubble, Douglas: The Dosage of Alkali, correspondence, Lancet **2**: 634 (Sept. 14) 1935.

22. Eusterman, G. B., and Balfour, D. C.: The Stomach and Duodenum, Philadelphia, W. B. Saunders Company, 1935, p. 288.

23. Wilkinson, S. A., and Jordan, Sara M.: The Significance of Alkalosis in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **1**: 509 (Sept.) 1934.

24. Jordan, Sara M., and Kiefer, E. D.: Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, Am. J. Surg. **15**: 472 (March) 1932. Bockus, H. L., and Bank, Joseph: Alkalosis and Duodenal Ulcer, M. Clin. North America **16**: 143 (July) 1932. Shattuck, H. F.; Rohdenburg, E. L., and Booher, Lela E.: Antacids in the Medical Management of Peptic Ulcer, J. A. M. A. **82**: 200 (Jan. 19) 1924. Way, C. T., and Muntwyler, Edward: Alkalosis: Clinical Problem, Ann. Int. Med. **8**: 818 (Jan.) 1935. Berger and Binger.[30] Oakley.[7] Hardt and Rivers.[4] Eisele.[18]

25. Nicol, B. M.: The Renal Changes in Alkalosis, Quart. J. Med. **9**: 91 (Jan.) 1940. Gatewood, Gaebler, Muntwyler and Myers.[6] Cooke.[11] Wildman.[10] Cope.[12] Footnote 24.

26. These include, among others, Hardt and Rivers.[4] Jordan.[7] Jeghers and Lerner.[31]

27. McCance, R. A., and Widdowson, E. M.: Alkalosis with Disordered Kidney Function, Lancet **2**: 247 (July 31) 1937. Footnote 7.

28. Wilkinson and Jordan.[23] McCance and Widdowson.[27] Footnote 7.

29. Brown, G. E.; Eusterman, G. B.; Hartman, H. R., and Rowntree, L. G.: Toxic Nephritis in Pyloric and Duodenal Obstruction: Renal Insufficiency Complicating Gastric Tetany, Arch. Int. Med. **32**: 425 (Sept.) 1923. Gamble, J. L., and Ross, S. G.: Factors in Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1**: 403 (June) 1925. Gollwitzer-Meier, K.: Tetanie Studien: III. Die Magentetanie, Ztschr. f. d. ges. exper. Med. **40**: 83, 1924. Steinitz, H.: Ueber chloroprive Tetanie bei Magenerkrankungen, Ztschr. f. klin. Med. **107**: 560, 1928. Meyer, Paul: "Urämie" infolge langdauernden Erbrechens, Klin. Wchnschr. **10**: 155, (Jan. 24) 1931.

in 5 of this group. It is of interest to note that the urea clearance decreased during calcium carbonate therapy in 8 patients without alkalosis, an observation reported also by McGee and his associates.[9] In 4 the clearance had been previously either low or at the lower limit of normal. However, the drop in values varied from 10 to 15 per cent and was of no clinical significance.

There have been relatively few studies reported in the literature on the status of renal function after the subsidence of alkalosis. The evidence available [30] indicates that the kidneys usually recover completely their normal function within several weeks or two to three months. Cope reported the case of a man who had experienced four severe attacks of alkalosis. The renal function, estimated by the urea clearance method, after recovery from the fourth attack was 92 per cent. Jeghers and Lerner,[31] Steele [32] and Berger [33] have noted that in occasional patients the lowered renal function may persist for some time. In the present series, renal function returned to its original level in 23 of 25 patients (table 2). This improvement was noted usually within seven to fourteen days after the onset of treatment. In some patients recovery occurred within two to three days, while in 3 cases one, three and six months elapsed before recovery was complete.

## TREATMENT

Alkalosis, regardless of cause, is invariably associated with a decrease in the serum chlorides. This relationship is explained by the fact that the total base concentration of the serum is maintained at a relatively constant level. The total base is combined for the most part with chloride and bicarbonate ions and, consequently, a change in the concentration of one of these cations causes a compensatory and inverse alteration in the concentration of the other. In this manner, a normal electrolyte content and normal osmotic pressure of the blood are preserved.[34] Hartwell and Hoguet [35] apparently were the first to use physiologic solution of sodium chloride in the alkalosis of experimental intestinal obstruction, although the beneficial results were attributed by these authors to the administration of fluids. The specific value of sodium chloride in relieving the metabolic disturbance in pyloric and high intestinal obstruction was subsequently established in numerous experimental and clinical studies.[36] The use of sodium chloride in the treatment of alkalosis during alkali ingestion likewise has been found highly effective, although the discontinuance of alkalis undoubtedly has played a major role in the recovery of these patients. Wildman and Gatewood, in fact, attributed a large proportion of the symptoms of uncompensated alkalosis to the hypochloremia. It has been recognized for some time that the clinical and chemical manifestations of experimental and human salt deficiency [37] closely resemble those of alkalosis arising during alkali therapy. In view of these considerations it seemed to us probable that in calcium carbonate alkalosis the hypochloremia might be the primary factor. If this were true, the addition of sodium chloride should suffice to correct the acid-base balance despite the continuation of alkali. The first opportunity to test this assumption arose in the following case:

## REPORT OF CASES

CASE 1 (chart 1).—R. F., a man aged 24, a travel agent, entered the hospital after a severe massive hemorrhage from a duodenal ulcer. On the seventh day of calcium carbonate therapy, acid-base studies revealed a mild alkalosis which

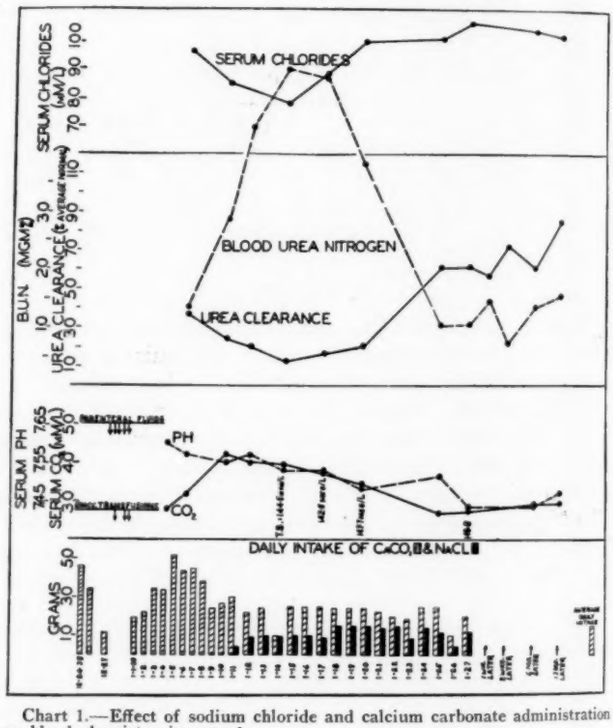


Chart 1.—Effect of sodium chloride and calcium carbonate administration on blood chemistry in case 1.

became severe four days later. Sodium chloride was added to the program on the twelfth day. Despite the continuation of calcium carbonate, the acid-base balance gradually improved and returned to normal after fourteen days of added sodium chloride therapy. The blood urea nitrogen dropped from a peak of 54.7 mg. per hundred cubic centimeters to 10.4 mg. per hundred cubic centimeters, and the urea clearance rose from 13 per cent to 61 per cent of average normal. The patient has shown no further signs of alkalosis despite continued calcium carbonate therapy for a period of two years. The urea clearance is now 85 per cent, and the blood urea nitrogen is 15.3 mg. per hundred cubic centimeters.

30. Berger, E. H., and Binger, M. W.: The Status of the Kidneys in Alkalosis, J. A. M. A. **104:** 1383 (April 30) 1935. Cooke.[11] Cope.[12] Nicol.[25]

31. Jeghers, Harold, and Lerner, H. H.: The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer: Report of Cases with a Review of the Pathogenesis, Clinical Aspects, and Treatment, New England J. Med. **214:** 1236 (June 18) 1936.

32. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkalis: Report of Case, J. A. M. A. **106:** 2049 (June 13) 1936.

33. Berger, E. H.: Importance of Kidney Function in Alkalosis, Northwest Med. **36:** 125 (April) 1937.

34. Peters and Van Slyke: Quantitative Clinical Chemistry,[13] vol. 1, p. 1031.

35. Hartwell, J. A., and Hoguet, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59:** 82 (July 13) 1912.

36. These include among others:
MacCallum, W. G.; Lintz, J.; Vermilye, H. N.; Legett, T. H., and Boas, E.: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, Bull. Johns Hopkins Hosp. **31:** 1 (Jan.) 1920.
Dixon, C. F.: The Value of Sodium Chloride in the Treatment of Duodenal Intoxication, J. A. M. A. **82:** 1498 (May 10) 1924.
Walters, Waltman, and Bollmann, J. L.: Experimental Acute Gastric Fistula, Arch. Surg. **13:** 578 (Oct.) 1926.
Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Acute Intestinal Obstruction Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes, Am. J. M. Sc. **173:** 649 (May) 1927.

37. These include among others:
Frouin, A.: Action des chlorures de l'alimentation sur la sécrétion gastrique, Presse méd. **30:** 1096 (Dec. 20) 1922.
Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93:** 407 (June) 1930.
Borst, J. G. G.: Urämie durch Kochsalzmangel, Ztschr. f. klin. Med. **117:** 55, 1931.
McCance, R. A., and Widdowson, E. M.: The Secretion of Urine in Man During Experimental Salt Deficiency, J. Physiol. **91:** 222 (Nov. 26) 1937; ibid.[54]
Poll, Daniel, and Stern, J. E.: Untoward Effects of Diuresis with Special Reference to Mercurial Diuretics, Arch. Int. Med. **58:** 1087 (Dec.) 1936.
Lyall, Alexander, and Nicol, Bruce M.: Gastric Secretions in Hypochloraemia, J. Physiol. **96:** 21 (June 14) 1939.

As a result of these observations, 27 patients with alkalosis during the administration of calcium carbonate have been treated similarly. The quantity of sodium chloride prescribed varied from 3 to 15 Gm. daily, although the minimum effective dose seems to be about 5 Gm. Clinical improvement promptly occurred in all 27 patients. The acid-base balance returned to normal within three to fourteen days. The urea clearance, as noted previously, returned to original levels in all but 2 patients. However, the restoration of a normal electrolyte equilibrium did not take place as rapidly as it does when alkalis are discontinued in addition to the administration of fluids and sodium chloride.

The following case further demonstrates that, even in severe alkalosis, the addition of sodium chloride to the program may correct the acid-base disturbance despite the continued use of calcium carbonate:

CASE 2 (chart 2).—M. W., a woman aged 68, a housewife, had complained of symptoms of ulcer for eleven years. She had been treated at the University Clinics for nine years, during which time alkalis had been taken periodically. Her blood pressure fluctuated between 198 systolic and 100 diastolic and 210 systolic and 100 diastolic, but renal function (urea clearance and concentration tests) was normal. Prior to entry into the hospital, the patient had vomited repeatedly. Roentgenograms revealed marked pyloric stenosis. Severe alkalosis was noted on the fifth day of therapy. The urine contained occasional hyaline casts; its specific gravity was 1.026. Sodium chloride was added to the program on the sixth day, the alkali being continued. The acid-base balance and renal function returned to normal after ten days of sodium chloride treatment. In the following year the patient showed no evidence of alkalosis despite the continued use of calcium carbonate. The degree of pyloric stenosis lessened, and nightly gastric aspirations now yield only small amounts.

## COMMENT

The mechanism of the alkalosis described in this series of patients is not entirely clear, although it is probable that more than one factor is involved. As noted previously, antecedent renal damage was not present in the majority of cases. It has been suggested [38] that part of the carbonate ion may be absorbed into the blood, thereby disturbing the acid-base balance. Although the total base values did not exceed normal limits, this possibility must be definitely considered. Cooke has suggested also that insoluble salts may "fix" the gastric juice, thus preventing the normal neutralization of alkaline intestinal secretions and making available for absorption an increased quantity of base. Evidence to confirm or deny these assumptions would be extremely important. The fact that sodium chloride corrected the acid-base imbalance despite continued ingestion of calcium carbonate suggests that we are dealing with primary hypochloremia. There is good reason to believe that the Sippy regimen tends to produce in some patients, at least, a chloride deficiency. Thus the daily intake of sodium chloride by these patients was estimated to be 2.33 Gm., as compared with the average normal intake of 10 to 12 Gm. Chloride depletion is particularly marked in persistent vomiting, as demonstrated in several of the cases. A further source of chloride loss is the aspiration of gastric contents, one of the routine procedures in the Sippy program. In this manner, several hundred milligrams of chloride may be removed daily; this removal, in a patient already on a low chloride intake, may be distinctly detrimental. The loss of chloride by this method is considerably greater in patients with pyloric stenosis and gastric retention. The quantity of gastric contents removed in the 2 patients described previously averaged from 200 to 400 cc. daily; in the entire group with alkalosis the nightly aspirations exceeded 200 cc. in 17 of the 32 patients. However, it is difficult to explain entirely on this basis the absence of acid-base disturbances in five persons whose aspirations exceeded 200 cc. daily and the occurrence of alkalosis in 2 patients in whom aspiration was not done. Kiefer has attributed the increased frequency of alkalosis, when gastric hypersecretion is present, to the loss of chloride resulting from increased sodium excretion. Another possibility is that calcium carbonate may remove large amounts of chloride from the gastric juice, some of which may not be reabsorbed. Binger and Goldschmidt [39] have shown

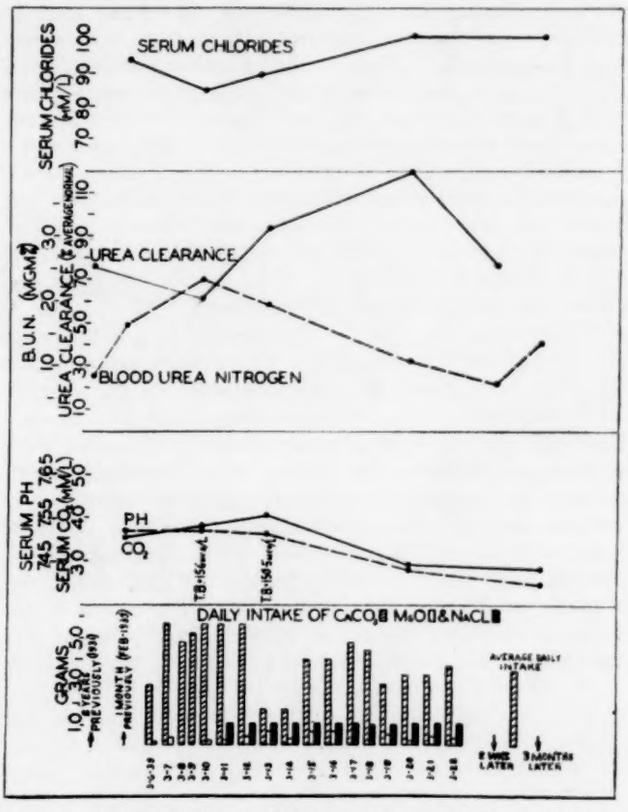


Chart 2.—Effect of sodium chloride and calcium carbonate administration on blood chemistry in case 2.

that calcium lactate in increasing concentration first accelerates, then inhibits the absorption of chlorides from solutions of sodium chloride in the intestine. Studies in progress on this problem [40] indicate that the feces contain larger amounts of chloride after ingestion of calcium carbonate than in control periods, although it is doubtful that this chloride loss is of primary significance. The question of intestinal absorption of chlorides is obviously a complicated problem since, as Lyall [41] pointed out, intestinal secretions contain up to 0.64 per cent of sodium chloride while the chloride concentration of the intestinal contents for absorption is of the same order. It is probable, however, that the loss of chloride is of importance chiefly as a contributory factor, since in 73 patients on a similar

38. Peters, J. P.: Personal communication to the authors. Cope.[12]

39. Binger, C. A. L., and Goldschmidt, S.: Studies in the Mechanism of Absorption from the Intestine: VI. The Colon; the Influence of Calcium Salts upon the Absorption of NaCl in the Intestine, Am. J. Physiol. **48**: 473 (May) 1919.

40. Kirsner, J. B.: Unpublished studies.

41. Lyall, Alexander: The Pathology of Chloride Metabolism in Man, Brit. M. J. **2**: 760 (Oct. 14) 1939.

regimen alkalosis did not develop. In 11 of these, however, the serum chloride decreased several millimols during calcium carbonate therapy. The problem may be related to differences in gastric secretion, variations in the salt intake and salt reserve of the body, and varying plasma volumes prior to treatment. In this connection, 1 patient with alkalosis had worked near blast furnaces and, although he perspired profusely, did not take the sodium chloride tablets which were available.

The rapid improvement in renal function after the use of sodium chloride in these patients is of considerable interest. It has been recognized for some time that decreased renal function is a regular concomitant of hypochloremia. Romalo and Dumitresco [42] observed in 1914 that the blood urea nitrogen was higher in nephritis during periods of reduced salt intake than in periods when the diet contained more salt. Chabanier and Lobo-Onell,[43] Host [44] and Landis and his associates [45] have also noted a decrease in renal function during periods of reduced salt intake. These observations were not confirmed by Cope,[46] who apparently produced only a mild chloride deficiency. Many investigators, especially the French,[47] have expressed the belief that the decrease in chlorides directly impairs renal function and is directly responsible for the acute rise in nonprotein nitrogen. This theory has been disputed by Kerpel-Fronius,[48] Clausen [49] and others,[50] who attributed the so-called "azotemia" to a withdrawal of sodium and its sequelae. Extrarenal azotemia, in fact, has been produced experimentally in the absence of hypochloremia.[51] Likewise one of us (J. B. K.) has been able to produce experimentally hypochloremia without azotemia.[52] The volume of extracellular fluids cannot be maintained without normal amounts of sodium and chloride; consequently, the loss of these ions is invariably accompanied by a decrease in the extracellular fluid, or dehydration.[53] McCance [54] has actually found a reduction of 28 to 38 per cent in the volume of body fluids in experimental human salt deficiency. Although measurements of the fluid balance in 4 out of 6 of our patients did not reveal any significant changes in the urinary output prior to and during alkalosis (the fluid intake and output increased somewhat after the addition of sodium chloride) dehydration may well have been present in these patients. Indeed, dehydration may occur even though the total body water remains unchanged, for the intracellular content of fluid may be increased at the expense of the extracellular fluid.[55] Renal function is usually decreased in dehydration.[53] McCance and Widdowson have observed a fall in the creatinine, sucrose, inulin and urea clearances in experimental salt deficiency. The lowered renal efficiency has been attributed to a reduction in the rate of glomerular filtration, which may itself result from a combination of factors. These include increased colloidal osmotic pressure of the blood, decreased blood volume, increased blood viscosity, a reduction in the number of "active" glomeruli (due to the decreased blood volume) and a decreased rate of circulation.[56] In fact, Gömöri and his co-workers [57] have demonstrated a reduction in the rate of circulation and a decrease in filtration pressure under similar conditions. The lowered urea clearances described in the present study suggest that renal failure was due either to a decreased renal blood flow or to a less complete extraction of urea from the blood. Since the renal tubules function best when the serum concentration of electrolytes is normal,[58] it is possible also that decreased tubular efficiency may be responsible in part for some of the changes. The importance of dehydration is further indicated by the fact that severe acute alkalosis may be produced experimentally without impairment of urea and creatinine clearances when care is taken to avoid depletion of fluid.[59] The elevated blood urea nitrogen does not necessarily indicate renal failure in the pathologic sense;[60] it is due to the decreased renal function and perhaps to increased tissue catabolism during dehydration.[61]

The beneficial effect of sodium chloride on renal function in the patients discussed is an indirect one and seems to be related entirely to the correction of dehydration. Thus, sodium chloride makes it possible to increase the volume of extracellular fluids by extracting water from the cells and by increasing the intake of fluids.

The augmented plasma volume, as Gömöri,[57] Berenzon [62] and others [63] have shown, improves renal function by increasing the rate of circulation and the rate of glomerular filtration.

## SUMMARY AND CONCLUSIONS

Alkalosis developed in 32 of 105 patients who received calcium carbonate in the treatment of peptic ulcer. The tendency to alkalosis was not related to

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53. Gamble, J. L.: Dehydration, New England J. Med. **201:** 909 (Nov. 7) 1929; Extracellular Fluid, Bull. Johns Hopkins Hosp. **61:** 174 (Sept.) 1937.

54. McCance, R. A.: The Effect of Salt Deficiency in Man on the Volume of the Extracellular Fluids and on Composition of Sweat, Saliva, Gastric Juice, and Cerebrospinal Fluid, J. Physiol. **92:** 208 (March 14) 1938.

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56. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934, p. 40. Gömöri, Podhradszky and Kring.[57] McCance and Widdowson.[37] Clausen.[49]

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the quantity of calcium carbonate prescribed. Symptoms usually appeared within three to eight days after the onset of treatment and consisted of a distaste for milk and cream, excessive dryness of the mouth and throat, anorexia, dizziness, headache, nausea and vomiting. There was no correlation between the severity of symptoms and the degree of chemical alkalosis. The carbon dioxide combining power and $p_H$ were elevated and the serum chlorides were markedly lowered during alkalosis. The total base in 12 patients with a normal acid-base balance and in 8 patients with alkalosis did not exceed normal values. The serum calcium was not elevated except in 1 patient. Neither anemia nor hepatic disease was of etiologic significance. The urea clearance was normal in 22 of 32 patients prior to the onset of alkalosis. Twelve patients with reduced urea clearances did not show any acid-base disturbance. The urea clearance decreased in 25 patients during alkalosis. In 9 cases the clearances fell below 20 per cent of average normal. The blood urea nitrogen rose concomitantly, reaching a peak of 67.6 mg. per hundred cubic centimeters in 1 case. In 2 patients the urine during alkalosis contained traces of albumin. In a third case, the urine was acid and contained albumin, casts and red blood cells. Renal function returned to original levels in 23 of the 25 patients within seven to fourteen days after the onset of treatment. In 3 cases recovery occurred only after one, three and six months had elapsed.

A total of 27 patients with alkalosis during the administration of calcium carbonate were treated by the addition of sodium chloride, the alkali being continued. Clinical improvement was prompt in all cases and, despite the continued use of calcium carbonate, the acid-base balance returned to normal within seven to fourteen days. The mechanism of the alkalosis following the administration of calcium carbonate has not been conclusively established. Chloride deficiency seems to be the most important factor although absorption of carbonate ions may play a role. Hypochloremia may be due to (*a*) low intake of sodium chloride, (*b*) loss of chloride from vomiting or from the aspiration of the gastric contents and (*c*) increased excretion of chloride in the feces. However, other factors as yet unknown are involved since, in this series, alkalosis did not develop in 73 patients on a similar regimen. The reduced renal function is probably due to dehydration with consequent decrease in the rate of glomerular filtration. The beneficial effect of sodium chloride on the acid-base balance and on renal function, despite the continued use of calcium carbonate, is due to the correction of hypochloremia and to the establishment of a normal water balance.

Alkalosis after the administration of calcium carbonate is primarily due to a deficiency of chloride and to consequent dehydration. The alkalosis may be combated successfully by the administration of adequate quantities of sodium chloride and fluid even though the ingestion of calcium carbonate is continued. However, the most effective means of treating alkalosis still remains the discontinuance of alkali in addition to the administration of adequate amounts of sodium chloride and fluid.

Renal function, as measured by the urea clearance test, is usually markedly depressed during alkalosis but returns to its previous level after the electrolyte balance is restored.

## ABSTRACT OF DISCUSSION

DR. DANA W. ATCHLEY, New York: Clinically it is worth while to point out the incorrectness of the common concept that calcium carbonate is an inert substance and may be used as effective alkali without disturbing the acid-base equilibrium. That concept is a common one. I was not clearly aware of it. One of the reasons that we haven't noticed much of this is that in New York, at least at the Presbyterian Hospital, we are not quite so enthusiastic about the use of alkalis. We treat many cases of ulcer with diet alone and without the introduction of alkali or drainage (never with gastric drainage). The clinical picture described is not one that is associated with the other types of alkalosis with which one is familiar. It is a picture that could well be associated with dehydration, and I should like to ask the authors whether, during the course of their observation of these patients, they carried out any sequential determination of hemoglobin or serum protein percentage or daily weights which would give some index as to whether or not there had occurred a dehydration sufficient to produce the renal effects that they observed or sufficient to produce the clinical picture. Such findings, if present, would explain the therapeutic benefit of sodium chloride. I want to express my appreciation of the instructive nature of this clinical contribution. When I come to the chemical side I hardly know where to begin. Too many of my treasured concepts have been overthrown. The degree of alkalosis from purely a point of view of the $p_H$ of the circulating plasma is amazing. The authors present figures with which I am not familiar and which are extraordinary in the degree, quantitatively, with which this alkalosis has actually disturbed the hydrogen ion concentration. This is a tremendous upset toward the alkaline side. It is difficult to understand this effect of calcium carbonate. Calcium chloride is a diuretic which I have always felt acted because it produced an acidosis, a genuine acidosis with loss of carbon dioxide and a true change of $p_H$ to the acid direction. I assumed that that was due to the fact that calcium formed insoluble salts and was removed, excreted entirely or almost entirely by the intestinal tract, in that way freeing the chlorine to act as an acid ion. If that is true, one would expect an analogous disturbance with calcium carbonate, although carbonic acid is a much weaker acid than hydrochloric acid.

DR. L. C. GATEWOOD, Chicago: When Haden and Orr first showed that the intravenous or subcutaneous use of sodium chloride would correct alkalosis I began that treatment when alkalosis occurred in the course of ulcer management, particularly when associated with obstruction. It was manifest that, if the patient was not vomiting, the intake of chloride by mouth should have the same effect as the intravenous or subcutaneous use. As long as ten years ago I used the same technic which Drs. Kirsner and Palmer described, giving sodium chloride by mouth in doses of 5 to 10 Gm. a day and have verified what he has reported. There are some interesting sidelights on this which bear on the question of alkalosis and other body chemistry. It is related probably to a depletion of chlorides from the body, and in just what way I do not think has been determined. In the treatment of a patient with duodenal ulcer and pyloric obstruction, alkalosis developed. Hydrochloric acid secretion in the stomach promptly disappeared. Alkali was stopped and chloride was given to correct the alkalosis. There was no immediate return of hydrochloric acid secretion, although acid-base equilibrium was promptly brought back to normal, and the patient continued without hydrochloric acid secretion for a period of three months. Then secretion gradually returned to normal. After a time she was again given a few doses of alkali (calcium carbonate and sodium bicarbonate) and promptly her hydrochloric acid again disappeared and a slight degree of alkalosis recurred, immediately corrected with sodium chloride. I have made similar observations on a number of occasions. The exact demonstration of the chemistry involved in this is not at all simple, because it requires some means of determining chlorides other than the blood chloride. The blood chlorides on this regimen could be kept at about normal levels, so in order to solve the problem it is necessary to determine rather completely all the body losses of chloride and also to make some

determinations of tissue chloride. It is suggested that possibly determination of spinal fluid chloride might yield some light on this in the same way that determinations of calcium content in the spinal fluid and comparison of those with the blood calcium shed light on calcium storage a number of years ago.

DR. E. N. COLLINS, Cleveland: The work of Haden and Orr has been mentioned. Naturally association for a number of years with Dr. Haden at the Cleveland Clinic has made me "chloride conscious." Urinary chloride determinations have proved significant in the treatment of alkalosis. In our experience these determinations give more accurate values relative to the acid-base balance of the patient than the blood chloride determinations. General practitioners who do not have a blood chemistry laboratory at their disposal can easily make those determinations. In patients who have pyloric obstruction, in addition to giving the usual parenteral therapy to overcome dehydration I routinely give a 3 per cent solution of hypertonic sodium chloride intravenously, usually 500 cc. in 5 per cent dextrose solution once or twice during the twenty-four hour period. The solution is given very slowly and is checked by daily determinations of the urinary chloride. An attempt is made to keep the urinary chlorides above 5 Gm. in twenty-four hours. When or if the obstruction is relieved, sodium chloride is given by mouth if the urinary chloride determinations do not show normal findings by that time. One feature about the presentation of Drs. Kirsner and Palmer that surprises me is the length of time it takes to bring these patients back to a normal acid-base balance. In my experience giving hypertonic saline solution intravenously in cases in which there is obstruction for three or four days suffices.

DR. JOSEPH B. KIRSNER, Chicago: We also were puzzled by the chemistry of calcium carbonate when this first became known to us, and through correspondence with various men in the East we learned that others also were puzzled. The question of dehydration is of paramount importance. We are undertaking a study to settle that question. I might cite from the literature, however, McCann's work demonstrating in alkalosis a reduction in the volume of extracellular fluid of approximately 28 to 38 per cent. We have determined the hemoglobin frequently and have not been impressed by any marked changes. I have not tabulated the daily weights, although we have those data available. As far as the $p_H$ being too high is concerned, I should point out that the $p_H$ of 7.73 was only one observation of many; in our laboratory we are inclined to place less reliance on the $p_H$ than any other feature of the acid-base balance, because as a colorimetric method it is subject to many technical errors. The question of the absorption of calcium carbonate is extremely interesting. We have been carrying out metabolic studies on this point and I can say positively at this time that after the administration of calcium carbonate the urinary calcium increases from two to five times that in the precalcium carbonate period. The explanation is not yet apparent. I should like to point out that Dr. Gatewood was among the first to indicate the relation between hypochloremia and alkalosis, and we have drawn on his writings frequently. In other experiments we have been able to reduce the chlorides in animals from 115 millimols per liter to 38, determining the $p_H$ of the gastric juice and the total chlorides, and have found no significant variation. This observation has also been made previously by other workers. The difficulty of giving sodium chloride in large enough amounts has been an individual problem. We found certain patients in whom 5 Gm. was not enough and we have had to increase the amount to 10 Gm. daily; the second patient required about 20 Gm. The question of spinal fluid chloride is important. In two cases of alkalosis reported in the *Lancet* the spinal fluid chlorides were found to be reduced in a measure similar to that found in the blood. Dr. Gatewood's suggestion about chlorides other than blood chlorides is another matter which we intend to look into. In our group of patients with alkalosis there were some whom we might classify as having pyloric stenosis, but I should like to make it clear that the majority did not have pyloric stenosis. As to the length of time for the return to normal of the electrolyte balance, of course, when one gives sodium chloride intravenously the return to the acid-base balance will take place in several days.

# SEQUELAE OF SEVERE DISEASE OF THE ABDOMINAL VISCERA

## WITH SPECIAL REFERENCE TO PSYCHONEUROSIS AND IMBALANCE OF THE AUTONOMIC NERVOUS SYSTEM

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It is my purpose in this paper to inquire into a group of cases of psychoneurosis whose origins date to an attack of irritative disease of the abdominal viscera of such severity as to have been associated with the probability of imminent death, or which are associated with diseases of the abdominal viscera characterized by a chronic course of increasing severity. In this group are cases of peptic ulcer with massive hemorrhage, ruptured peptic ulcer, surgical intervention in peptic ulcer with extremely stormy postoperative course, severe typhoid with delirium, carcinoma of the gastrointestinal tract, cases of poisoning by mouth with associated gastroenteritis and similar diseases having in common the factors of irritation and of extreme gravity of outcome in some part of their course.

These conditions are met in the course of neuropsychiatric practice and are variously diagnosed as psychoneurosis, neurasthenia, autonomic imbalance or neurocirculatory asthenia. In the more severe form there is such quick development of exhaustion that the normal occupation cannot be pursued at all or in any event is greatly restricted. The patient gives the impression of still being in a convalescent period long after the acute illness is over.

Subjectively, there are feelings of inadequacy associated with apprehension and mild depression. There are complaints of awareness of the heart beat, breathlessness after slight exertion or excitement and quick development of fatigue on slight exertion. On physical examination there are an irritable pulse rate, vasomotor changes in the hands and feet, myotatic irritability, hyperactive muscular reflexes, increased axillary perspiration, low blood pressure, occasionally subnormal temperature or alterations of the normal temperature rhythm. With laboratory studies there may be found a lowered basal metabolic rate and abnormal blood sugar tolerance curves with a tendency to hypoglycemic reaction.

### RELATIONSHIP OF PATHOLOGIC ALTERATIONS IN THE CENTRAL NERVOUS SYSTEM TO SYMPTOMS

The evidence for organic changes in the central nervous system accompanying diseases of the abdominal viscera may be considered in two phases: first, pathologic alterations accompanying the acute phase of the visceral disease and secondly, the healing of such pathologic alterations with resultant scarring and consequent disturbances of function.

In 1881, Wernicke [1] gave an extremely lucid account of the symptoms, signs, clinical course and autopsy in 3 patients who presented in common punctate hemorrhage in the walls and floor of the third ventricle, the massa intermedia of the thalamus and occasionally

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Read before the Section on Nervous and Mental Diseases at the Ninety-First Annual Session of the American Medical Association, New York, June 12, 1940.

1. Wernicke, Carl: Lehrbuch der Gehirnkrankheiten für Aerzte und Studierende, Berlin, Theodor Fischer, 1881, p. 229-242.

the gray matter of the aqueduct of Sylvius and of the fourth ventricle. He summarized the characteristic clinical manifestations as follows: (1) disturbance of consciousness, (2) somnolence or agitation followed by somnolence, (3) reeling gait, (4) partial to complete paralysis of the eye muscles and (5) inflammatory (hemorrhagic) changes in the retina.

Wernicke's first case was that of a 20 year old seamstress who had taken sulfuric acid by mouth. No history of alcoholism was noted. The characteristic signs appeared, and the illness ran a course of forty-one days. At autopsy there was noted a stenosis of the pylorus, gastrectasis and chronic ulceration of the stomach. In the walls of the third ventricle there were numerous small hemorrhages distributed on both sides. Similar hemorrhages occurred in the massa intermedia of the thalamus. In this case hemorrhages were not noted in the corpora quadrigemina of the midbrain or in the cerebellum, but the hemorrhages occurred in the retina. Wernicke designated the neuropathologic diagnosis "Encephalitis haemorrhagica substantiae griseae ventricul. III."

The other 2 cases of Wernicke were associated with alcoholic psychosis (delirium tremens). In both cases hemorrhages occurred in the hypothalamus as well as in the gray matter of the aqueduct of Sylvius and in the floor of the fourth ventricle, especially localized in the calamus scriptorius. It is noteworthy that Wernicke did not in any way limit the disease to association with severe alcoholism, although in subsequent years the error was made and some authors specifically limited the term first used by Wernicke, "acute hemorrhagic polioencephalitis superior," to those cases occurring with alcoholism. It appears clear from Wernicke's description that he attempted to build a clinical entity, based on hemorrhagic findings in the brain stem, entirely analogous to that occurring in the spinal cord in acute anterior poliomyelitis. For this reason, apparently, he emphasized the findings in the somatic motor nuclei (especially those to the eye muscles) whereas these are not at all constant even in the alcoholic form, while somnolence, alterations of consciousness and emotion are invariably present. Acute anterior poliomyelitis became a disease ascribable to an infectious agent while acute hemorrhagic polioencephalitis superior remains a pathologic complex occurring with many different conditions; for this reason it is desirable to use some such term as Wernicke's encephalopathy [2] to designate the characteristic pathologic findings.

*Acute Encephalopathy.*—In every one of 14 patients with peptic ulcer who came to autopsy, hemorrhages in the anterior hypothalamus, massa intermedia and the medial wall of the dorsal thalamus have been observed. In 7 of the cases in which the medulla was examined, hemorrhage was noted also in the dorsal motor nucleus of the vagus. An alcoholic history was prominent in only 2 of the cases. Nine of the cases were associated with perforation of the ulcer and peritonitis, 2 cases with continuous slow bleeding, 2 cases with bronchopneumonia after gastroenterostomy and 1 with massive hemorrhage into the gastrointestinal tract. Two of the cases were associated in their terminal stage with hyperglycemia and glycosuria.[3]

Somewhat similar hemorrhages were found in other cases of irritative disease of the abdominal viscera: tuberculous peritonitis, typhoid, carcinoma of the cervix uteri with fistula into the bladder and rectum, and poisoning with saponated solution of cresol. In a series of cases of carcinoma of the stomach recent and healed hemorrhages were also found. In a group of 20 control cases which included instances of cardiac failure, carcinoma of the lung, malignant hypertension, Addison's disease and acute bacterial endocarditis, hemorrhagic changes were not noted. Of 20 cases of diabetes mellitus, hemorrhages in the hypothalamus occurred in 9.

The following case, briefly summarized, will serve as an illustration of the foregoing discussion:

CASE 1.—*Chronic duodenal ulcer; perforation; peritonitis.*

A white man aged 59 presented complaints over a period of three years of indigestion and frequent attacks of pain after eating. He was not addicted to alcohol. There was a sudden attack of severe cramping pain in the abdomen, and the patient was transferred to the Hamilton County Chronic Disease Hospital on the following day, at which time he was already desperately ill. The abdominal muscles were rigid. The temperature was 102.5 F. There was repeated vomiting. The heart presented extrasystoles. The pulse rate, which was 128 on entrance to the hospital, became progressively more rapid, so that counting was impossible. The patient died the day after entrance into the hospital.

On autopsy there was found a perforated duodenal ulcer and acute generalized fibrinopurulent peritonitis. Serial sections

Fig. 1 (case 1).—Multiple hemorrhages are present in the oral portion of the dorsal motor nucleus of the vagus nerve. Involved in the hemorrhages are preganglionic neuron cell bodies to the stomach and duodenum and cell bodies of the nucleus cardiacus (Malone). Morgan's stain. Slightly reduced from a photomicrograph with a magnification of 16 diameters.

of the entire brain stem and diencephalon as well as several cortical areas, after staining and microscopic study, revealed multiple hemorrhages limited to the following structures: (1) oral portion of the dorsal motor nucleus of the vagus (fig. 1), (2) superior and anterior portion of the hypothalamus at the level of the nucleus paraventricularis, especially in the region between the fornix and the hypothalamic sulcus and (3) the massa intermedia of the thalamus involving cells of the nucleus paramedianus and nucleus reuniens complex. There were no hemorrhages in the corpora quadrigemina, the mamillary bodies of the nuclei of the third, fourth and sixth cranial nerves.

The tendency of hemorrhages of the Wernicke type to occur with diseases of the gastrointestinal tract is well substantiated from the literature. Wernicke's [1] first case, ulceration of the stomach associated with sulfuric acid poisoning, has been noted. Roemer [4] called attention to the role of botulism developing in the course of ptomaine poisoning by meat, sausage, fish and oysters and accompanied clinically by paralysis

2. Campbell, A. C. P., and Biggart, J. H.: Wernicke's Encephalopathy (Polioencephalitis Haemorrhagica Superior): Its Alcoholic and Non-alcoholic Incidence, J. Path. & Bact. **48**: 245-262 (March) 1939.

3. Vonderahe, A. R.: Histopathologic Changes in the Nervous System in Cases of Peptic Ulcer, Arch. Neurol. & Psychiat. **41**: 871-912 (May) 1939.

4. Roemer, Paul: Textbook of Ophthalmology in the Form of Clinical Lectures, translated by M. L. Foster, New York, Rebman Company, 1913, pp. 611-613.

of the eye muscles and other cerebral manifestations. Sträussler [5] described 2 cases occurring during the course of obstruction of the bowel. Harmes [6] in a discussion of alcoholic forms of Wernicke's encephalitis noted the frequent occurrence of chronic gastritis in these cases and suggested that some form of gastrointestinal intoxication may be an important factor. The characteristic pathologic findings have also been noted in puerperal fever, bilateral sarcoma of the kidneys and typhoid.[7] Campbell and Biggart [2] reported 12 cases of Wernicke's encephalopathy, of which 3 were associated with gastric carcinoma, 1 with an old gastroenterostomy, 2 with hyperemesis gravidarum and one with chronic pyosalpinx. These findings, of course, do not exclude the fact that hemorrhagic phenomena have been observed in some other conditions—vitamin $B_1$ deficiency,[8] hypochloremia,[9] fatal ether anesthesia [10] and, as noted previously, in occasional cases of diabetic acidosis.

*Subacute and Chronic Encephalopathy.*—Clinically, it is known that people suffering from visceral abdominal disease of such gravity as to present some of the

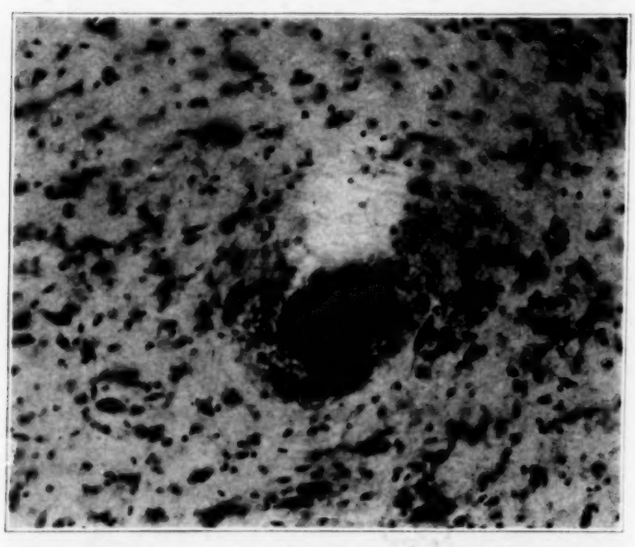

Fig. 2 (case 2).—An older hemorrhage is present in the anterior hypothalamus. There are present some degeneration of red blood cells, deposits of pigment and an area of parenchymatous degeneration. Morgan's stain. Reduced from a photomicrograph with a magnification of 130 diameters.

signs of Wernicke's encephalopathy sometimes recover. In the alcoholic form recovery occurs occasionally but not completely, a defect in the psychic sphere tending to persist.[6] These observations are borne out by demonstrable anatomic changes.

In the 14 cases of peptic ulcer noted previously, 4 patients with chronic gastric ulcer and 1 with gastric ulcer with malignant change (adenocarcinoma) presented in the anterior hypothalamus partly disintegrated red blood cells and evidence of glial proliferation. In 2 of the aforementioned cases glial proliferation and particles of pigment were also noted in the oral part of the dorsal motor nucleus of the vagus. In a series of cases of carcinoma of the stomach there occurred in the hypothalamus, in association with more recent hemorrhagic changes, areas of pale-staining red blood cells, disintegrated red blood cells and occasionally evidence of glial replacement.

These observations may be illustrated in the following case:

CASE 2.—*History.*—A white woman aged 59 was a resident, with her sister, of the Hamilton County Home. For approximately six months prior to her death there was noted a loss of weight and an increasing amount of weakness, so that the patient required to be constantly helped by her sister. She was not, however, given to complaining, and aside from the progressive exhaustion there were few or no subjective symptoms. She was taken suddenly ill with an attack of severe nausea and vomiting and was transferred on the following day to the Hamilton County Chronic Disease Hospital.

*Physical Examination.*—On admission the pulse rate was 120, the respiratory rate was 30 and the blood pressure was 80 systolic and 50 diastolic. Examination of the abdomen revealed some rigidity and a questionable mass in the epigastrium. There was continuous vomiting. Six hours after admission the patient showed a decided change for the worse. The pulse rate dropped to 60. There was mental confusion and delirium. Six hours later the pulse rate was barely perceptible and the heart sounds were scarcely audible. The pulse continued to be slow and scarcely perceptible until death.

*Postmortem Examination.*—The autopsy revealed coronary sclerosis with acute myocardial infarction, which was regarded as the primary cause of death. In addition there was found a deep ulcer on the inferior wall of the stomach with thickened and indurated margins involving the mucous membrane of the body of the stomach above the pylorus. Microscopic sections through this area revealed that, in addition to the ulcer, malignant changes (adenocarcinoma) were present. Examination of serial sections through the diencephalon revealed small hemorrhages in the hypothalamus at the level of the paraventricular nucleus. The hemorrhages extended caudally to implicate the cells of the nucleus reuniens complex in the massa intermedia, together with the nucleus paramedianus of the thalamus. In addition to these fresh hemorrhages, older hemorrhages were found in the hypothalamus close to the hypothalamic sulcus. The old hemorrhages were characterized by disintegrated red blood cells, deposits of iron pigment (staining characteristically with Turnbull's blue and prussian blue) and local degeneration of the parenchyma (fig. 2). There was only slight phagocytic reaction. However, there were areas of patchy, intense gliosis (fig. 3) surrounding blood vessels, especially in the preoptic region of the thalamus.

*Comment.*—This case, in its pathologic aspects, presents evidence of hemorrhagic phenomena apparently occurring at different intervals of time. The case is of especial interest because death from myocardial infarction occurred suddenly.

Neubürger [11] presented evidence of healing of the hemorrhages characteristic of Wernicke's encephalopathy in its nonalcoholic forms. The author studied the hypothalamus and brain stem in 6 cases of carcinoma of the stomach, 1 of carcinoma of the head of the pancreas, 1 of sarcoma involving the liver and mucosa of the stomach and 1 of chronic atrophic gastritis. In addition to fresh hemorrhage, Neubürger found frequent evidence of perivascular blood casts and glial replacement, proliferated blood vessels with small areas of degeneration and areas of blood pigment around the blood vessels. His observations were amplified in a subsequent study of the central nervous system in chronic gastritis.[12] In alcoholic forms, Bender and

5. Sträussler, cited by Harmes,[6] p. 10.

6. Harmes, Theodor: Klinischer und anatomischer Beitrag zur Lehre von der Poliencephalitis acuta hämorrhagica superior, Neumünster, Germany, R. Hieronymus, 1911.

7. Claude, Henri, and Lévy-Valensi: Maladies du cervelet et de l'isthmi de l'encéphale, Paris, J. B. Baillière et fils, 1922, p. 299.

8. Alexander, Leo: Wernicke's Disease: Identity of Lesions Produced Experimentally by $B_1$ Avitaminosis in Pigeons with Hemorrhagic Polioencephalitis Occurring in Chronic Alcoholism in Man, Am. J. Path. **16**: 61-70 (Jan.) 1940.

9. Larson, C. P.: Fatal Cases of Acute Manic-Depressive Psychosis, Am. J. Psychiat. **95**: 971-982 (Jan.) 1939.

10. Uchimura, Yushi: Clinical and Pathologic Studies of the Diencephalon, Psychiat. et neurol. jap. **40**: 55-57 (Oct.) 1936; abstracted, Arch. Neurol. & Psychiat. **39**: 164 (Jan.) 1938.

11. Neubürger, Karl: Ueber die nichtalkoholische Wernickesche Krankheit, inbesondere über ihr Vorkommen beim Krebsleiden, Virchows Arch. f. path. Anat. **298**: 68-86, 1936.

12. Neubürger, Karl: Wernickesche Krankheit bei chronische Gastritis: Ein Beitrag zu den Beziehungen zwischen Magen und Gehirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**: 208-225, 1937.

Schilder [13] presented numerous instances of reaction to hemorrhage with phenomenon of healing. They pointed out significantly (p. 1048) that the vascular lesions have in general the same distribution as the glial ones but invade more deeply. They also pointed out the presence of capillary budding and proliferative changes in the blood vessels involving both the endothelial and adventitial layers but noted that the absence of inflammatory response is remarkable. They emphasized the electivity of the lesions for vegetative gray masses along the ventricles.

### PROGNOSIS AND TREATMENT

While the phenomena of hemorrhage are associated with severity and gravity of the clinical course and many of the patients die, there is evidence, pathologically, of progressive stages of healing of the acute lesions and, clinically, that some patients survive. It is not remarkable that among those who survive there should be some who present the residual effects of injury to central autonomic centers. Peptic ulcer has been more completely studied with respect to end results than any other form of abdominal visceral disease. That a diminution of working capacity may occur after severe peptic ulcer has been noted by Meyer and Scher.[14] In a study of the results in 500 cases of ruptured peptic ulcer by Thompson,[15] 51 patients were followed from three to fifteen years; complete relief was obtained after operation in 38.7 per cent and incomplete relief in 61.2 per cent; some type of subsequent therapeutic care was required in all but 12 cases; inability to work for varying periods after operation was experienced in 42.8 per cent. In 2 patients of the group total disability was present.

The treatment of sequelae of severe irritative disease of the abdominal viscera is based on pathologic considerations. The psychotherapy depends on the recognition of an organic handicap traceable to lesions in the central autonomic centers. With this in mind the patient is asked to face the reality of a disability. Since many of the patients are suffering from a depression based on unsuccessful efforts at maintaining too high a level of mental and physical exertion, the resolution of the mental conflict is usually accomplished without difficulty. The irritable pulse rate and respiratory rate require increased physical rest. The metabolic and autonomic symptoms such as hypoglycemic episodes and hypochlorhydria are readily treated symptomatically. Inasmuch as Leo Alexander [8] has shown the similarity of the hemorrhagic lesions in these cases to those produced by $B_1$ avitaminosis, thiamine hydrochloride is administered in liberal quantities. As a prophylactic measure administration of thiamine hydrochloride for a period of time before the abdominal operation is suggested.

The following clinical case report illustrates the application of some of the foregoing observations:

CASE 3.—*History.*—An unmarried white woman aged 38 complained of pronounced exhaustion and anxiety. There was a mild depression based on the belief that she was lacking in character and will power because she was unable to continue teaching a two hour class in sewing. She also complained of palpitation and breathlessness after slight exertion, excessive perspiration, occasional dull headaches and pronounced sleeplessness.

She was in good health until the onset of acute ruptured appendicitis at the age of 20. There was an extremely stormy postoperative period, requiring hospitalization for six weeks. At the age of 22 a resection for bowel obstruction was performed. At the age of 24 a gastroenterostomy was done for hemorrhage from a gastric ulcer; the postoperative period again was extremely stormy with a hospital stay of seven weeks. There was blurring of vision for several months. After six months of convalescence the patient attempted to work as a teacher, but the distress and fatigue were so great that she required rest for long periods in order to go on. The patient dated her present difficulties in large part to this illness.

At the age of 28 there developed in the patient excessive menstrual bleeding, and a hysterectomy was done. She again was dangerously ill; however, after repeated transfusions and other restorative measures, she recovered from the immediate operative effects although she remained in the hospital for three months in a state of invalidism. At the age of 35, because of various gastrointestinal complaints, an exploratory laparotomy was done and the gallbladder was removed; although local anesthesia was used there was extreme shock after the operation, and for several days death was regarded as imminent. The following year, a diagnosis of hyperthyroidism was made and a thyroidectomy was done under local anesthesia; immediately after this operation the patient suffered a psychosis characterized by excitement, excessive psychomotor activity and terror; restraint was required for several days, after which the psychotic manifestations subsided. The patient remained a semi-invalid thereafter, but some improvement occurred with complete rest. After approximately a year, however, having been told "to fight it through" and "to use will power," she attempted to return to her work teaching sewing to children. After three months characterized by progressive emotional and physical disability she presented herself for examination and treatment.

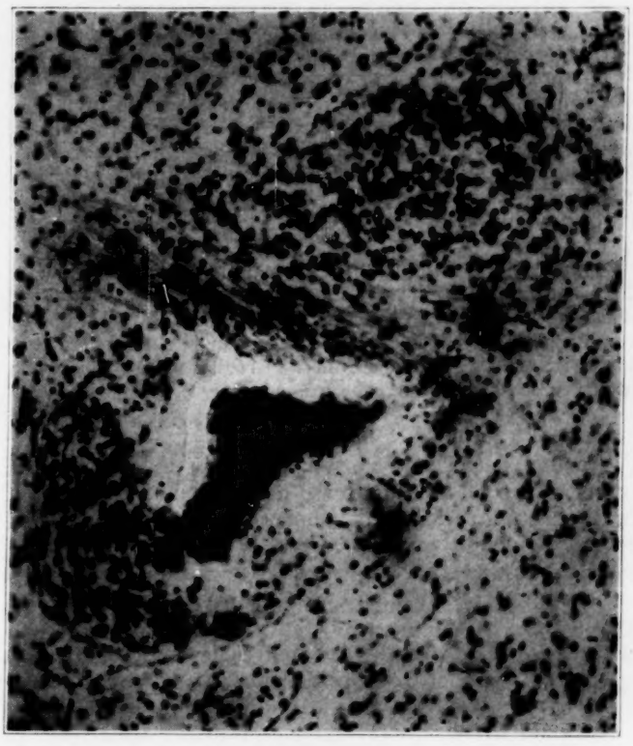

Fig. 3 (case 2).—An area of intense perivascular gliosis is present in the preoptic region of the hypothalamus. Morgan's stain. Reduced from a photomicrograph with a magnification of 130 diameters.

*Physical Examination.*—The patient presented an anxious, depressed appearance. She weighed 98 pounds (44.5 Kg.). The pulse rate, which was 68 in a recumbent position, rose to 90

13. Bender, Lauretta, and Schilder, Paul: Encephalopathia Alcoholica (Polioencephalitis Haemorrhagica Superior of Wernicke), Arch. Neurol. & Psychiat. **29:** 990-1053 (May) 1933.

14. Meyer, Jacob, and Scher, Eleanor: A Study of the Occupational Adjustment of Patients with Peptic Ulcer, Rev. Gastroenterol. **5:** 54-64 (March) 1938.

15. Thompson, H. L.: Acute Perforation of Peptic Ulcer: Immediate and Late Results in Five Hundred Cases, J. A. M. A. **113:** 2015-2018 (Dec. 2) 1939; personal communication to the author.

immediately after the patient sat up in bed. There was consistent hypothermia, with the temperature ranging from 97 F. to 97.8 F. The respiratory rate in bed ranged from 20 to 28. The blood pressure was 102 systolic and 64 diastolic. The dextrose tolerance test showed hypoglycemia, the sugar content being 45.1 mg. per hundred cubic centimeters at the end of the third hour. Gastric analysis revealed hypochlorhydria, the hydrochloric acid content of the gastric juice being 8 per cent. The basal metabolic rate was —2 per cent. The blood count and urinalysis were essentially normal; the Wassermann test gave negative results.

A diagnosis of psychoneurosis and neurasthenia with autonomic imbalance was made. The present illness was regarded as being consequent to healed hemorrhages (Wernicke's encephalopathy) located chiefly in the parasympathetic areas of the hypothalamus and medulla, permitting alterations of metabolism and a too ready release of sympathetic manifestations.

*Treatment and Course.*—The patient was told that she was suffering from an organic disability and was asked to accept the handicaps which it entailed. This helped to resolve the depression and some of the anxiety which were based on the belief that she was lacking in character because she could not accomplish the usual amount of work. After a preliminary rest in bed of two weeks, a program calling for ten hours of rest in bed at night and two hours of rest in bed after lunch was advised. Minimal amounts of pentobarbital sodium (½ grain, or 0.03 Gm.) were adequate for a full night's sleep. Diluted hydrochloric acid, 15 minims (0.92 cc.) with each meal, for the hypochlorhydria and vitamin $B_1$ (thiamine hydrochloride), 10 mg. daily, were ordered. A high caloric and high fat diet, with five meals a day, was utilized to correct the hypoglycemic trend.

With the measures instituted there was a gain in weight of 15 pounds (6.8 Kg.) in the following two months. Emotional disturbances subsided. Fatigue, breathlessness and palpitation continued to be in evidence after exertion but much less than formerly, and the patient was able to return to half-time work, at which she continues at the present time.

## CONCLUSIONS

Acute Wernicke's encephalopathy may occur with many forms of severe disease of the abdominal viscera, and chronic residual damage to the autonomic and metabolic areas of the central nervous system may persist. Such damage may be reflected in certain conditions variously diagnosed as psychoneurosis, neurasthenia, autonomic imbalance or neurocirculatory asthenia. The treatment is based on the psychotherapeutic procedure of permitting the patient to recognize an organic handicap, on a program of regulated rest and activity and on symptomatic treatment of metabolic disturbances and avitaminosis.

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## ABSTRACT OF DISCUSSION

DR. ROBERT G. GREEN, Minneapolis: I should like to call attention to the widespread occurrence of a disease similar to Wernicke's among animals which is definitely associated with the feeding of fresh fish. For years I have been attempting to learn about virus diseases by systematically studying fur-bearing animal populations, and one of the most devastating outbreaks of disease that I have encountered has been a disease that we called Chastek paralysis, as it was first recognized on the fox ranch owned by Mr. Chastek. After years of investigation we came to realize that this was a vitamin $B_1$ deficiency disease, and it appears to be identical with Wernicke's disease. Fur animal populations differ from a human population in that all individuals receive exactly the same diet. Records are complete, so that one can study the feeding records before and after the appearance of the disease. All these outbreaks have been associated with the feeding of fresh fish and often as a part of a diet that would appear to be quite adequate in vitamins, and especially vitamin $B_1$. I have also seen outbreaks occur where fox ranchers have fed their foxes rather large amounts of cod liver oil. We have consistently produced Chastek paralysis in foxes simply by adding 30 per cent of fish to what had been a diet adequate in all respects before. This indicates that in some way the feeding of raw fish may be associated with the destruction of vitamin $B_1$.

DR. NORMAN JOLLIFFE, New York: It is my belief that probably all the syndromes mentioned by Dr. Vonderahe represent one of the types of nutritional encephalopathy. The best defined of these has been labeled "nicotinic acid deficiency encephalopathy" (THE JOURNAL, Jan. 27, 1940, p. 307) and is characterized by clouding of consciousness, changing cogwheel rigidities of the extremities, and uncontrollable grasping and sucking reflexes. Another nutritional encephalopathy is one characterized by clouding of consciousness, cerebellar ataxia, ophthalmoplegia (complete or partial) and pupillary changes. I believe that the first syndrome represents an acute complete nicotinic acid deficiency, while the second represents an acute complete thiamine hydrochloride deficiency. More frequently than not one finds superimposed on these syndromes a delirious picture, a catatonic reaction, a cerebellar syndrome, or Korsakoff psychosis, in addition to polyneuropathy and the ordinary signs of pellagra. Under rare conditions each of these syndromes may occur alone, but usually two or more occur simultaneously, giving a confused clinical picture and a variety of pathologic findings. This confusion will persist as long as the combination of these syndrome is indiscriminately labeled under one diagnosis which varies with the hospitals and includes such terms as "wet brain," "central neuritis," "encephalopathy," "pseudo-Wernicke" and "Wernicke's disease." If ophthalmoplegia is present with one or more of the other syndromes I agree that the diagnosis of Wernicke's syndrome is justified. If ophthalmoplegia is not present I do not agree, however, with lumping together all the other nutritional encephalopathies under one label, such as "pseudo-Wernicke's." I believe that each patient should be labeled as to the clinical syndrome or syndromes presented, the response of each of the syndromes to specific crystalline vitamins recorded, and finally the pathologic changes found in each subject correlated with the clinical syndromes presented during life. If this is done it will eventually be possible to label each of these syndromes etiologically and anatomically and possibly administer the indicated specific nutritional substances necessary to initiate recovery.

DR. JOHN F. FULTON, New Haven, Conn.: I should like to ask Dr. Vonderahe what he considers the cause of the hemorrhagic lesions described. He has mentioned that, following acute abdominal episodes or associated with these episodes, hemorrhages are found. In long-standing cases evidence is present of old hemorrhage. Is it his opinion that the hemorrhage in the central nervous system precipitates the gastrointestinal crisis or that the gastrointestinal crisis through sensory innervation somehow irritates the centers in the hypothalamus and medulla and in that way secondarily causes the hemorrhage? I ask this because experimentally I have seen, following small lesions of the middle hypothalamic nuclei, acute petechial hemorrhages of the gastric mucosa, occasionally acute perforations and gastromalacia; and Dr. Zimmerman has reported a series of cases in which, following lesions of the central gray of the aqueduct, acute gastric hemorrhages occurred, or acute perforations. In the case of Dr. Zimmerman's evidence, the same question I suppose might be asked that I have asked Dr. Vonderahe: Which is cause and which is effect?

DR. A. R. VONDERAHE, Cincinnati: With respect to the role of vitamin $B_1$ deficiency, I think one application might be considered, namely the use of vitamin $B_1$ prior to operation as a prophylaxis against the production of such hemorrhages. I was interested in the comments of Dr. Jolliffe on terminology. It might be interesting to go back to the first description of these hemorrhagic findings by Wernicke himself, who was anxious, it seems, to build up a clinical entity comparable in the brain stem to that of anterior poliomyelitis in the spinal cord. For this reason he coined the term acute hemorrhagic polioencephalitis superior. But anterior poliomyelitis, as the years went on, was found to be a definite infectious disease, while so-called Wernicke's disease remains a pathologic complex producible by many different agents. Wernicke's first patient was not alcoholic; the other two that he described were alco-

holic. As time went on, the role of alcoholism was accentuated, so that one finds in some textbooks that the term "Wernicke's disease" is limited to alcoholism. Because of these factors, confusion has crept in. Wernicke's disease is not a characteristic disease entity. It occurs in alcoholism and it occurs, as we have seen here today, in a wide variety of other conditions. I am grateful to Dr. Fulton for asking this question. I believe that the recent hemorrhages in cases of gastric ulcer are effects. However, in patients who recover, the healed hemorrhages act as foci for a new cycle of autonomic disturbance. The cause of gastric ulcer is still undetermined. I think what I have to say can best be illustrated with a case which presented a history of gastric ulcer and at autopsy presented a gastric carcinoma. There were also small, bilateral, symmetrically placed meningiomas pressing on area 6, which, I would be inclined to think, may have caused the ulcer, while the changes occurring in the hypothalamus were secondary, perhaps associated with vitamin $B_1$ deficiency. I think that in the case of man we have to bear in mind the continuation of life once a disease is started. Man is not sacrificed when he develops an ulcer. His ulcer goes on, and its effects are reflected elsewhere in the altered condition of his body. These in turn produce other effects, and the cycle, which includes the changes in the central nervous system, continues onward until death.

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# THE USE OF DESICCATED PLASMA

## WITH PARTICULAR REFERENCE TO SHOCK

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Of the many problems in the field of surgery today, none are of more vital interest than the closely correlated problems of shock, fluid balance, blood volume and plasma proteins. The importance of this aspect of surgery has been emphasized by the present war and an urgent impetus imparted to its study.

In the belief that plasma proteins are the key to these surgical problems, this report of the results obtained by the operation of a routine desiccated plasma service is given. This service, operated in conjunction with the Baylor University blood bank during the last sixteen months, has made plasma of any desired concentration or amount available day or night in a manner comparable to ordinary intravenous fluids.

Our purpose in this paper in describing this service and its results is to point out the advantages and practicability of supplying concentrated plasma, prepared by redissolving the dry lyophilic form obtained through desiccation from the frozen state. We believe that plasma prepared in this manner exhibits in a greater degree not only all the desirable properties claimed for whole plasma but also unique additional advantages both technical and therapeutic, which are inherent in the desiccation and the concentration thereby made possible. The technical advantages of desiccation and concentration relating to storage, transportation, simplicity and speed of administration have been discussed in an earlier paper [1] on the new inexpensive desiccation method, the adtevac process. The importance of these practical technical factors should not be minimized, particularly in connection with military requirements.

However, the therapeutic advantages are even more significant and can be attributed chiefly to the control of osmotic forces made possible by choice of concentration up to four or five times normal. These advantages of concentrated plasma suggest three principal groups of indications: first, the regulation of blood volume; second, control of plasma protein levels, and third, special adjustment of fluid balance when marked hypertonic effects are essential.

Restoration of circulating blood volume is the essential aim of the treatment of shock, regardless of its cause, whether hematogenic, neurogenic, vasogenic or strictly posthemorrhagic. The part played by these causative factors is highly controversial and need not be considered here. However, there is general agreement with regard to the general mechanism of shock, namely a disparity in blood volume relative to vascular capacity. Blalock [2] and Moon [3] particularly have emphasized this point and stressed the importance of plasma loss from damaged capillaries. A vicious cycle tends to be set up, with progressive vascular damage resulting from anoxemia. The more profound the shock, the more urgent is the necessity for a speedy reversal of this mechanism before irreparable damage occurs.

As was previously indicated,[4] concentrated plasma appears ideal for this purpose for several reasons. First, larger amounts of protein can be more speedily placed in the circulation than by any other method, a point of importance in view of Minot and Blalock's [5] suggestion of the value of giving colloid fast enough to increase its level to the point of retaining effective circulating volume in spite of concomitant losses. Furthermore, hypertonic plasma tends to effect an immediate reversal of the abnormal physiologic changes of shock. Blood volume is built up by immediate withdrawal from the tissues of fluid previously lost from the blood stream. Finally it seems probable that concentrated plasma has a direct stimulating effect on vascular tone and permeability. King [6] showed increased effectiveness of hypertonic fluids in his work demonstrating the superiority of hypertonic over physiologic solution of sodium chloride, indicating direct vascular stimulation in shock cases. The work of Krogh and Harrop [7] and of Drinker [8] demonstrated the importance of plasma proteins or associated substances in the maintenance of capillary tone and normal permeability. The evidence suggested that the concentration of these substances was a favorable factor.

The second group of indications for plasma therapy is concerned with the control of plasma protein levels, a problem of increasing importance in modern surgery.

Aided by a grant from the Abbott Laboratories.

From the Department of Pathology, Hospital Laboratory Division, Baylor University College of Medicine.

1. Hill, J. M., and Pfeiffer, D. C.: A New and Economical Desiccating Process Particularly Suitable for the Preparation of Concentrated Plasma or Serum for Intravenous Use: The Adtevac Process, Ann. Int. Med. **14**: 201 (Aug.) 1940.

2. Blalock, A.: Principles of Surgical Care: Shock and Other Problems, St. Louis, C. V. Mosby Company, 1940.

3. Moon, V. H.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

4. Hill, J. M.: Intravenous Use of Concentrated Plasma Prepared by the Adtevac Process, Texas State J. Med. **36**: 223, 1940. Hill and Pfeiffer.[1]

5. Minot, A. S., and Blalock, A.: Plasma Loss in Severe Dehydration: Shock and Other Conditions as Affected by Therapy, Ann. Surg. **112**: 557, 1940.

6. King, R. A.: Methods of Fluid Administration in the Treatment of Surgical Shock: An Experimental Comparison, Brit. M. J. **2**: 485, 1940.

7. Krogh, A., and Harrop, G. A.: On the Substance Responsible for Capillary Tonus, J. Physiol. **54**: 125, 1921.

8. Drinker, C. K.: The Permeability and Diameter of the Capillaries in the Web of the Brown Frog (R. Temporaria) When Perfused with Solutions Containing Pituitary Extract and Horse Serum, J. Physiol. **63**: 249, 1927.

The quantities of protein required to combat hypoproteinemia make it highly desirable to give this type of intravenous feeding in concentrated form. By this means blood protein levels can be rapidly raised and sustained when suitable amounts are given. Furthermore, the work of Madden and Whipple [9] indicates not only that plasma is an ideal food for all cellular protein requirements but also that saturation of plasma protein storage depots is important in the production of antibodies.

In this connection we would also point out that prolonged preservation of antibodies, prothrombin and complement in plasma can be accomplished only by desiccation from the frozen state. The application of these facts to the treatment of infections by concentrated plasma is obvious.

The third group of indications for concentrated plasma involves special hypertonic effects required to accomplish substantial shifts of fluid. Reduction of increased intracranial pressure by concentrated plasma as reported by Hughes, Mudd and Strecker [10] is an example of such uses. For these purposes hypertonic plasma proteins are superior because of the prolonged osmotic effect. Surgical complications resulting from edema associated with hypoproteinemia logically fall in this group and show a rapid response to intravenous concentrated plasma. Ravdin [11] has reviewed this problem.

Experimental evidence of the value of concentrated serum in shock was first demonstrated by Bond and

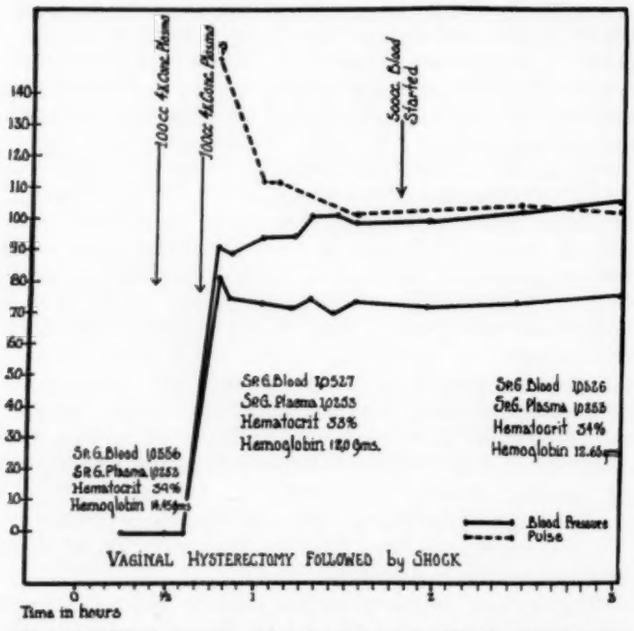


Chart 1.—Blood pressure and pulse in case 1. Blood pressure points have been plotted as 0 when the pressure was unobtainable by the ordinary methods.

Wright.[12] More recently Best and Solandt [13] found that concentrated serum was effective in the treatment of traumatic shock and hemorrhage in dogs. However, Magladery, Solandt and Best,[14] in a later report, denied any advantage of concentrated serum over an equal volume of whole serum in the treatment of post-hemorrhagic shock.

Clinical interest in the plasma proteins has been reflected chiefly in the expanding literature on the use of whole plasma. In the treatment of shock, reference should be made to the work of Levinson, Rubovits and

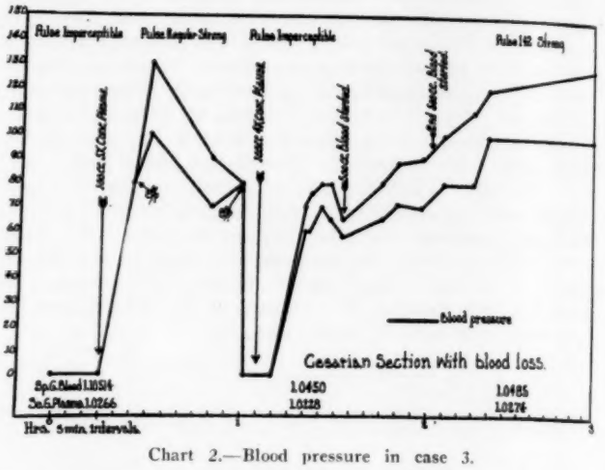


Chart 2.—Blood pressure in case 3.

Necheles,[15] of Strumia, Wagner and Monaghan [16] and of Brennan,[17] while in burns the reports of Elkington, Wolff and Lee,[18] of McClure [19] and of Minot and Blalock [5] are outstanding. This use of whole plasma represents a definite advance in the therapy of shock and burns. Nevertheless, we believe, full realization of all the potentialities of plasma proteins is possible only if choice of concentration is made available by desiccation.

The numerous reports on the use of whole plasma is in marked contrast to the restricted clinical use of concentrated plasma and serum. Hughes, Mudd and Strecker [10] in 1938 described the successful treatment of seven cases of increased intracranial pressure. No clinical reports in the field of surgery have since been observed which included any series of cases treated by concentrated plasma, although a preliminary summary of clinical results was given by Hill [4] and by Hill and Pfeiffer.[1] The treatment of nephrosis with concentrated serum, as emphasized by Aldrich and his associates,[20] represents an example of this type of therapy in the medical field. Hypertonic plasma has been used, however, in a variety of isolated cases included in the many papers on whole plasma.

## METHODS

Since in the past the chief obstacle to the use of concentrated plasma has been the technical difficulty

9. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20:** 194, 1940.

10. Hughes, Joseph; Mudd, Stuart, and Strecker, E. A.: Reduction of Increased Intracranial Pressure by Concentrated Solutions of Human Lyophile Serum, Arch. Neurol. & Psychiat. **39:** 1277 (June) 1938.

11. Ravdin, I. S.: Hypoproteinemia and Its Relation to Surgical Problems, Ann. Surg. **112:** 576, 1940.

12. Bond, D. D., and Wright, D. G.: Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lyophile Serum, Ann. Surg. **107:** 500, 1938.

13. Best, C. H., and Solandt, D. Y.: Use of Plasma or Serum as a Substitute for Whole Blood, Brit. M. J. **1:** 116, 1940.

14. Magladery, J. W.; Solandt, D. Y., and Best, C. H.: Serum and Plasma in Treatment of Hemorrhage in Experimental Animals, Brit. M. J. **2:** 249, 1940.

15. Levinson, S. O.; Rubovits, F. E., and Necheles, Heinrich: Human Serum Transfusions, J. A. M. A. **115:** 1163 (Oct. 5) 1940.

16. Strumia, M. M.; Wagner, J. A., and Monaghan, J. F.: Treatment of Secondary Shock, J. A. M. A. **114:** 1337 (April 6) 1940.

17. Brennan, H. J.: Plasma Transfusions in the Treatment of Hemorrhage, Brit. M. J. **1:** 1047, 1940.

18. Elkington, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, Ann. Surg. **112:** 150, 1940.

19. McClure, R. D.: The Treatment of a Patient with Severe Burns, J. A. M. A. **113:** 1809 (Nov. 11) 1939.

20. Aldrich, C. A.; Stokes, Joseph, Jr.; Killingsworth, W. P., and McGuiness, A. C.: Concentrated Human Blood Serum as a Diuretic in Treatment of Nephrosis: Preliminary Report, J. A. M. A. **111:** 129 (July 9) 1938. Aldrich, C. A., and Boyle, H. H.: Concentrated Human Blood Serum as a Diuretic in Nephrosis; Further Observations, J. A. M. A. **114:** 1062 (March 23) 1940.

of desiccation from the frozen state, it seems advisable to outline briefly the methods employed in our plasma service.

Plasma is obtained in part as a by-product of the blood bank and in part from blood taken directly for this purpose. A completely neutral plasma is produced by adsorption of agglutinins when the different types of whole blood are pooled at low temperature as described in an earlier paper.[21] It was found practicable to neutralize as much as ten parts of type O plasma with one part of type AB or one part each of types A and B whole blood. Edwards, Kay and Davie[22] have employed the same principle, but using only equal parts of A and B blood. When serum is used, the same technic is applied by defibrinating blood as it is drawn making cells and serum available.

The neutral plasma or serum is placed in large ampules of 500 cc. capacity and desiccated in bulk from the frozen state by the inexpensive adtevac process, by which moisture contents below 1 per cent are easily attained. At first the dry material was made into a four times concentrate and stored frozen in a low temperature refrigerator. Recently the dry material has been granulated in a special dispensing device, weighed and placed in vaccine type bottles. Either a vacuum is drawn or dry nitrogen introduced by way of a hypodermic needle, and the rubber cap sealed with celloidin. A dose of 25 Gm. is accompanied by sufficient water to make up 100 cc. of concentrate. All water used is strictly pyrogen free to avoid reactions.[23]

Practically all the plasma was given as the four times concentrate, a syringe of 50 or 100 cc. size and a 19 or 20 gage needle being used. On occasions when transfusions were already started the plasma was injected into the rubber tubing, which was temporarily clamped off above. In shock the dose was given rapidly, up to 100 cc. per minute. In other conditions the speed was judged by the apparent integrity of the cardiovascular system. Frequently an injection period of five minutes was satisfactory for the average 100 cc. dose. In cases in which a sudden increase of blood volume was considered dangerous, slower rates up to twenty minutes were recommended. Blood pressures were frequently checked during administration when very large amounts were given.

When possible, relative blood volume changes were followed by laboratory tests, such as blood and plasma specific gravity determinations, hematocrit, red cell count and photoelectric hemoglobin estimations.

TABLE 1.—*Summary of 111 Cases*

| | No. of Cases | No. of Doses | Total No. of Cc. | Average Dose |
|---|---|---|---|---|
| Shock prevention | 10 | 18 | 850 | 47 cc. |
| Hypoproteinemia | 23 | 49 | 4,605 | 94 cc. |
| Eclampsia and other obstetric conditions | 19 | 49 | 2,820 | 58 cc. |
| Severe infections and terminal collapse | 16 | 26 | 1,925 | 74 cc. |
| Neurosurgery and head injuries | 21 | 32 | 2,375 | 74 cc. |
| Burns | 6 | 15 | 1,320 | 89 cc. |
| Roentgen sickness | 3 | 7 | 355 | 50 cc. |
| Hemolytic anemia | 2 | 6 | 260 | 43 cc. |
| Miscellaneous | 11 | 10 | 845 | 85 cc. |
| Total | 111 | 299 | 15,355 | 68.2 cc. |

## CLINICAL DATA

The plasma service has been in operation approximately one and one-half years. During this period 22,220 cc. of four times concentrated plasma has been given to 156 hospital patients, while 8,295 cc. has been given to an undetermined number of outside patients, a total of 30,515 cc., requiring over one-fourth million cc. of blood for its preparation.

After removing the 45 closely followed cases of shock for separate analysis there remains a heterogeneous group of 111 cases summarized in table 1. It is not within the scope of this paper to report in detail the results of treatment in all the diverse conditions represented. However, it can be stated that no harmful effects were noted, some benefit was obtained in practically every case and impressive results were observed in several. The obstetric group including the successful treatment of eclampsia with hypertonic plasma will be reported elsewhere.

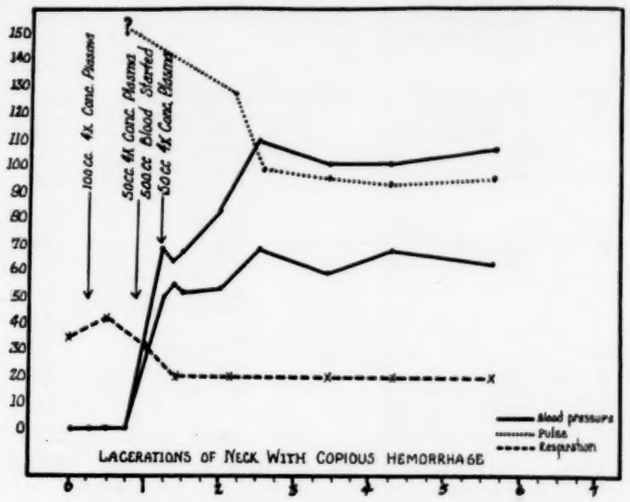


Chart 3.—Blood pressure, pulse and respiration in case 16.

Special mention should be made concerning the effects of concentrated plasma in surgical conditions other than shock. In complications associated with hypoproteinemia, such as saline edema, closure of anastomosis stomas, pulmonary edema and pneumonia, and retarded wound healing, concentrated plasma yielded excellent results in prevention and treatment.

The 45 cases of shock are summarized in table 2. Of this number 19 were considered as severe, 16 moderate and 10 mild. This classification, of course, is an arbitrary one based on criteria not as clear cut as could be desired. Severe cases were those with imperceptible pulse or blood pressure, or with profound mental depression on down to coma. Moderate cases were those presenting blood pressures definitely below the so-called critical level usually assumed to be 80 systolic and 40 diastolic. In mild cases the blood pressure was in the vicinity of this level with other signs of shock being exhibited. All cases showed the common signs of peripheral circulatory failure, namely sweating, pallor, cold clammy skin, mild cyanosis and rapid pulse.

The results of treatment were graded as excellent when the blood pressure was elevated above the critical level or higher in from five to thirty minutes, as fair when improvement was slower or less pronounced, and as poor when the response was transitory or absent. On this basis the results were excellent in 36 cases, fair in 8 and poor in 1. In this group of 45 cases some degree of hemorrhage was a factor contributing to shock in 36 instances. Some type of surgical procedure was performed in 37 cases, each not necessarily

21. Hill.[4]
22. Edwards, F. R.; Kay, J., and Davie, T. B.: The Preparation and and Use of Dried Plasma for Transfusion, Brit. M. J. **1**: 377, 1940.
23. Seibert, F. B.: Fever Producing Substances Found in Some Distilled Waters, Am. J. Physiol. **67**: 90, 1923.

TABLE 2.—*Observations in 45 Cases of Shock*

| Case | Age | Type of Case | Degree of Shock | Blood Pressure | Radial Pulse | Specific Gravity Blood | Specific Gravity Plasma | Hematocrit Hemoglobin | Amount 4× Concentrated Plasma | Other Measures | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 46 | Vaginal hysterectomy | Severe | Imperceptible<br>92/84<br>104/78 | Imperceptible<br>Just palpable<br>112 | 1.0556<br>1.0527 | 1.0252<br>1.0253 | 49%<br>14.45G<br>33%<br>12.00G | 200 cc. | 500 cc. blood after shock controlled | 100 cc., slight improvement; second 100 cc. and B. P. to 92/84 in 10 min., less restless; blood given and B.P. to 110/82, p. 108 |
| 2 | 34 | Two incidents:<br>(1) Hemorrhage from duodenal ulcer | Moderate | 68/55<br>108/75 | 92<br>weak<br>88 | 1.0536<br>1.0532<br>1.0498 | 1.0229<br>1.0235<br>1.0243 | 37%<br>34.5%<br>37% | 150 cc. | ..... | 100 cc., B. P. to 80/55 in 10 mins.; then 50 cc. and B. P. to 108/75 in 20 mins.; R. B. C. remained in vicinity of 3,670,000 |
| | | (2) Operation for the ulcer and hemorrhage | Severe | Imperceptible<br>88/44<br>Imperceptible<br>120/80 | Imperceptible<br>Weak<br>Imperceptible<br>140 | 1.0522<br>1.0519<br>1.0509 | 1.0277<br>1.0281<br>1.0234 | 37%<br>35.4%<br>36% | 230 cc.<br>380 cc. | 1,000 cc. whole blood being given when shock occurred | 350 cc. blood given when shock occurred; 100 cc., elevated B. P. to 88/44 in 5 mins.; 15 mins. later B. P. imperceptible; 65 cc. and repeated and B. P. to 80/? in 8 mins.; 90/70 in 20 mins.; later 120/80, P. 140, R. B. C. from 3,340,000 to 3,140,000 |
| 3 | 32 | Cesarean section; glomerulonephritis | Severe | Imperceptible<br>130/100<br>Imperceptible<br>110/80 | Imperceptible<br>Palpable<br>Imperceptible<br>140 | 1.0514<br>1.0450<br>1.0485 | 1.0265<br>1.0228<br>1.0274 | 31%<br>25%<br>25% | 350 cc. | 1,000 cc. blood | 150 cc. 2 days before operation; shock at operation, 100 cc. gave temporary results; a second 100 cc. and B. P. from imperceptible to 80/70 in 10 mins.; 1,000 cc., blood and B. P. to 110/80 |
| 4 | 66 | Copious hemorrhage during removal of large adenocarcinoma of kidney | Severe | Imperceptible<br>85/50<br>110/76 | Imperceptible<br>134<br>strong<br>100 | 1.0516<br>1.0497<br>1.0352 | 1.0241<br>1.0259<br>1.0210 | 28%<br>24% | 150 cc. | 500 cc. blood and 500 cc. saline after shock controlled | 100 cc. and B. P. to 85/50 in 10 mins.; 1½ hrs. later B. P. 40/?; then 40 cc. and B. P. to 74/50 in 20 mins.; later B. P. 110/76; R. B. C. in vicinity of 2,670,000 |
| 5 | 29 | Hemorrhage, post partum, profuse | Severe | 68/40<br>94/70<br>120/80 | 104<br>weak<br>Stronger<br>Strong | 1.0529<br>1.0478 | 1.0282<br>1.0238 | 34%<br>27% | 165 cc. | 500 cc. blood and 1,000 cc. 5% dextrose in saline after shock controlled | Semicomatose, B. P. 68/40; 100 cc. and in 5 mins. B. P. 75/60; in 20 mins. B. P. 94/70; later 120/80 |
| 6 | 45 | Breast operation and hemorrhage | Severe | .....<br>130/80<br>110/72 | Imperceptible<br>Strong<br>88 | 1.0463<br>1.0434<br>1.0380 | .....<br>1.0231<br>Very low | ....<br>30%<br>22% | 155 cc. | 700 cc. 5% dextrose in saline just before and shortly after concentrated plasma | No pulse, cold, pale, sweating, B. P. not taken; 100 cc. and in 10 mins. B. P. 130/80; later 55 cc. and B. P. 110/72 |
| 7 | 20 | Prolonged labor, no excessive bleeding | Severe | 70/?*<br>100/74<br>124/84 | Imperceptible<br>140<br>132 | 1.0428<br>1.0438<br>1.0340 | ..... | .... | 200 cc. | ..... | 90 cc. and B. P. to 80/? in 10 mins.; 110 cc. and B. P. to 96/76 in 5 mins.; later B. P. 124/84 |
| 8 | 25 | Perforated appendix; spinal anesthesia | Severe | 40/?<br>90/55<br>106/65 | Imperceptible<br>120<br>140 | 1.0488<br>1.0484<br>1.0496 | 1.0246<br>1.0276<br>1.0275 | .... | 110 cc. | Ephedrine with no results | After 110 cc., B. P. to 80/60 in 5 mins., to 90/55 in 9 mins. |
| 9 | 27 | Bullet wounds through chest | Severe | 65/30<br>94/60<br>114/84 | 140<br>140<br>130 | 1.0632<br>1.0608<br>1.0581 | 1.0276<br>1.0281<br>1.0285 | .... | 180 4×<br>100 5×<br>—<br>280 cc. | 500 cc. 5% dextrose in saline with no response | 80 cc. and B. P. to 75/50 in 30 mins.; 100 cc. and B. P. to 94/60 in 35 mins.; 8 hrs. later B. P. 96/60 and 100 cc. 5× conc. given; B. P. to 114/84 in 3 hrs. |
| 10 | 5 mos. | Spina bifida, myelomeningocele, operation | Severe | ..... | Imperceptible<br>Palpable<br>regular | ..... | ..... | .... | 18 cc. | 40 cc. saline by hypodermoclysis after shock controlled | Pulse imperceptible; sweating, cyanotic, condition considered critical; 18 cc. and in 5 mins. pink, ceased sweating; in 10 mins. pulse palpable |
| 11 | 48 | Pelvic operation, bulky fibroleiomyoma of uterus | Severe | 75/60<br>110/80<br>60/?<br>110/80 | 110<br>weak<br>120<br>120<br>110 | ..... | ..... | .... | 100 cc. | 1,000 cc. 5% dextrose in saline followed by shock; 500 cc. blood | 50 cc., B. P. to 110/80 in 10 mins.; additional 50 cc.; 50 mins. later B. P. 60/?, blood helped elevate it to 110/80 |
| 12 | 42 | Vaginal hysterectomy followed by shock | Severe | Imperceptible<br>70/?<br>Imperceptible | Imperceptible<br>Just palpable<br>Imperceptible | ..... | ..... | .... | 170 cc. | 1,000 cc. blood and 1,000 cc. saline | Shock 1½ hrs. after operation with gradual onset; slight temporary improvement with each dose; patient died |
| 13 | 45 | Carcinoma of cervix with hemorrhages | Severe | 50/30<br>105/80<br>100/70 | Imperceptible<br>80<br>90 | ..... | ..... | .... | 100 cc. | 1,000 cc. 5% dextrose in saline | Clinical improvement before much saline taken; B. P. to 105/80 in 30 mins.; later 50 cc. maintained B. P. at 100/70 |
| 14 | 40 | Lung abscess with lobectomy | Severe | Imperceptible<br>Not taken<br>76/60<br>100/60 | Imperceptible<br>130<br>104<br>110 | ..... | ..... | .... | 100 cc. | 500 cc. blood and 500 cc. saline | During operation 2,000 cc. saline and 500 cc. blood given; 30 mins. later sweating, pale, cold, unable to get B. P. or pulse; 100 cc. with blood, B. P. 76/60, 3½ hrs. later; later 100/60 |
| 15 | 23 | Ruptured tubal pregnancy | Severe | Imperceptible<br>72/44<br>Normal | Imperceptible<br>Weak<br>84 strong | ..... | ..... | .... | 75 cc. | 500 cc. blood and 500 cc. saline | Deep shock, 75 cc. and B. P. from imperceptible to 60/? in 5 mins., to 68/40 in 20 mins., to 72/44 in 40 mins.; then blood given and B. P. normal, pulse 84 |

* Question mark signifies that only few impulses heard and no definite diastolic level discernible.

TABLE 2.—*Observations in 45 cases of Shock—Continued*

| Case | Age | Type of Case | Degree of Shock | Blood Pressure | Radial Pulse | Specific Gravity Blood | Specific Gravity Plasma | Hematocrit Hemoglobin | Amount 4× Concentrated Plasma | Other Measures | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | 55 | Lacerations of neck with copious hemorrhage | Severe | Imperceptible<br>70/50<br>100/58 | Imperceptible<br>Palpable<br>94 | ..... | ..... | .... | 300 cc. | 500 cc. blood and 500 cc. saline | Comatose, cyanotic, sweating, cold, B. P. and pulse imperceptible, respirations sporadic; 100 cc. and began to move, sweating ceased; 100 cc. more, 500 cc. blood started and in 25 mins. B. P. 70/50; in 1 hr. B . P. to 100/58; next day 50 cc. and B. P. stabilized |
| 17 | 19 | Fracture of right femur and laceration | Severe | 75/?<br>118/65 | 160 weak<br>140 strong | ..... | ..... | .... | 200 cc. | 500 cc. blood and 500 cc. saline | On admission B. P. 125/70, pulse 88; patient restless and 100 cc. given; while 500 cc. blood given, patient into shock; 100 cc. and B. P. to 90/20 in 10 mins., to 88/50 in 25 mins., to 118/65 in 1 hr. |
| 18 | 21 | Head injury, subarachnoid hemorrhage, compound fracture | Severe | 40/?<br>60/30<br>110/70<br>Imperceptible | Imperceptible<br>Just palpable<br>Strong<br>Imperceptible | ..... | ..... | .... | 255 cc. | ..... | Severe shock, 100 and 75 cc. doses, in 20 mins. B. P. 60/30, in 30 mins, 110/70; 1 hr. later B. P. and pulse imperceptible, and 2 hrs. later patient died |
| 19 | 53 | Malaria, history of blood in stool and vomitus | Moderate | 60/?<br>70/50<br>92/70 | 100<br>96<br>88 | 1.0579<br>1.0519 | 1.0214<br>1.0210 | 46%<br>15.55G<br>40%<br>13.25G | 150 cc. | 500 cc. blood | 500 cc. blood and 30 cc. and B. P. to 64/50 in 25 mins.; 5 mins. after 70 cc., B. P. 70/50; 50 cc. more and B. P. 92/70; later 120/70 |
| 20 | 18 | Operation, spinal fusion | Moderate | 55/20<br>70/54<br>80/60 | Imperceptible<br>120<br>116 | 1.0527<br>1.0510<br>1.0491 | .....<br>.....<br>..... | 41%<br>13.55G<br>11.75G<br>12.35G | 190 cc. | ..... | 50 cc. in O. R., gradual response; 50 cc., B. P. to 70/54 in 45 mins.; third 50 cc. and B. P. 76/60; 90 cc., B. P. to 80/60, later 110/80 |
| 21 | 41 | Radical mammectomy | Moderate | 64/ no change<br>80/50<br>64/30<br>94/64 | 150 weak<br>140 stronger<br>140<br>144 | 1.0478<br>1.0427 | 1.0295<br>..... | 30%<br>7.9G<br>24% | 150 cc. | ..... | 100 cc. and B. P. to 80/30 in 9 mins., then down to 64/30 7 min. later; 50 cc. and B. P. to 80/55 in 20 mins.; later 94/64 and 110/70 |
| 22 | 18 | Cervical dissection for malignant melanoma | Moderate | 65/?<br>85/45<br>110/70 | Weak and fast<br>Stronger<br>126 | 1.0613<br>1.0597<br>1.0532 | 1.0299<br>1.0298<br>1.0254 | 38%<br>35%<br>32% | 100 cc. | 1,000 cc. 5% dextrose in saline followed by shock | 100 cc. and B. P. to 85/45 in 15 mins.; in 20 mins. 95/60, to 110/70 35 mins. after given |
| 23 | 91 | Hemorrhage, about 1,000 to 1,500 cc. lost | Moderate | 80/70<br>130/74 | Weak<br>Strong | 1.0594<br>1.0559 | 1.0273<br>1.0262 | 36%<br>36% | 100 cc. | 500 cc. blood and 500 cc. saline after shock controlled | 50 cc. and B. P. to 100/70 in 20 mins.; 50 cc. more and B. P. to 130/74 |
| 24 | 32 | Multiple fractures of pelvis and right leg | Moderate | 50/40<br>80/50<br>100/60 | 98<br>80<br>80 | 1.0547<br>1.0530<br>1.0528 | 1.0260<br>1.0258<br>1.0258 | 40%<br>31%<br>31% | 55 cc. | 1,000 cc. 5% dextrose in saline started at same time plasma given | In 10 mins. B. P. to 65/45; in 2½ hrs. 86/54, later 120/70; R. B. C. 4,000,000 to 3,300,000 |
| 25 | 23 | Multiple fractures and lacerations | Moderate | 78/48<br>115/72 | Weak<br>90<br>strong | 1.0635<br>1.0529 | 1.0270<br>1.0291 | .... | 150 cc. | 500 cc. blood after shock controlled | 50 cc. given because of mounting blood sp. gr.; 1 hr. later B. P. 78/48; 100 cc. and B. P. 115/92 in 15 mins. |
| 26 | 16 | Operation, open reduction | Moderate | 84/?<br>94/52<br>100/70 | Imperceptible<br>Imperceptible<br>150 | 1.0639<br>1.0609<br>1.0570 | 1.0311<br>1.0314<br>1.0303 | .... | 100 cc. | ..... | Shock; B. P. 84/? but in 2 hrs. B. P. 94/52; 100 cc. and B. P. to 100/70 in 20 mins. |
| 27 | 40 | Pelvic operation, hysterectomy and salpingectomy | Moderate | 60/?<br>94/70<br>108/80 | Imperceptible<br>128<br>120 | 1.0589<br>1.0583 | 1.0312<br>1.0303 | .... | 100 cc. | 500 cc. blood and 500 cc. saline | Shock after all of blood taken; 50 cc. and B. P. to 90/? in 20 mins.; then 50 cc. and B. P. to 94/70 15 mins. later; in 2½ hrs. B. P. 108/80 |
| 28 | 18 | After normal delivery with about 700 cc. blood loss | Moderate | 80/50<br>110/60<br>115/70 | Weak<br>148<br>... | 1.0490<br>1.0480<br>1.0426 | 1.0274<br>1.0276<br>1.0251 | .... | 200 cc. | 500 cc. blood and 500 cc. saline | Semicomatose, cold, sweating; 100 cc. and B. P. from 80/50 to 110/60 in 10 mins.; later 100 cc. and B. P. from 125/80 to 130/80 7 mins. later |
| 29 | 34 | Abdominoperineal resection of rectum | Moderate | 60/?<br>75/40<br>100/64<br>100/60 | Imperceptible<br>160<br>136<br>124 | 1.0522<br>1.0485<br>1.0440 | ..... | .... | 250 cc. | 1,000 cc. 5% dextrose in saline followed by shock; later 1,000 cc. blood and 1,000 cc. saline | 50 cc. elevated B. P. from 60/? to 75/40 in 10 mins.; 50 cc. more and B. P. 100/64 in 1½ hrs.; then 1,000 cc. saline and 50 cc. 4× conc. plasma; later blood and 100 cc. more given; R. B. C. from 4,150,000 to 2,650,000 |
| 30 | 15 | Removal of large thoracic neuroblastoma | (1) Moderate | 80/60<br>105/80 | Weak<br>Strong | ..... | ..... | .... | 100 cc. | 500 cc. blood and 500 cc. saline | Shock immediately after operation; 100 cc. elevated B. P. to 105/80 in 25 mins.; 500 cc. blood and B. P. 100/70 for 2 days |
| | | | (2) Moderate | 85/60<br>105/60<br>100/70 | Questionable<br>Stronger<br>162 | ..... | ..... | .... | 100 cc.<br>—<br>200 cc. | 500 cc. blood and 500 cc. saline | Two days later shock, 100 cc. and B. P. to 105/60 in 20 mins.; B. P. remained 90/60 to 100/70 |

TABLE 2.—*Observations in 45 Cases of Shock—Concluded*

| Case | Age | Type of Case | Degree of Shock | Blood Pressure | Radial Pulse | Specific Gravity Blood | Specific Gravity Plasma | Hematocrit Hemoglobin | Amount 4× Concentrated Plasma | Other Measures | Comment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 31 | 39 | Pelvic operation, endometriosis | Moderate | 74/60<br>96/60<br>112/78 | Imperceptible<br>140<br>120 | 1.0520<br>1.0494<br>1.0494 | 1.0246<br><br>1.0246 | .... | 70 cc. | 500 cc. blood after shock controlled | 70 cc., B. P. to 96/60 in 10 mins.; later 112/78; R. B. C. 3,990,000 to 3,500,000 |
| 32 | 52 | Hemorrhage, copious after prostatic reaction | Moderate | 80/40<br>130/75 | Weak<br>Strong | ..... | ..... | .... | 100 cc. | 2,000 cc. blood, 500 cc. saline and shock persisted | After 2,000 cc. blood patient remained pale, cold, sweating, very weak pulse; 100 cc. improved condition promptly |
| 33 | 57 | Hysterectomy and appendectomy | Moderate | 80/50<br>134/84 | Fast, weak<br>84 | ..... | ..... | .... | 100 cc. | 500 cc. blood and 500 cc. saline | 1,000 cc. 5% dextrose in saline followed by shock; blood elevated B. P. to 110/60; 50 cc. and B. P. to 134/84; 50 cc. more and B. P. to 174/98 |
| 34 | 34 | Bilateral salpingo-oophorectomy | Moderate | 70/35<br>106/55 | Very weak<br>130<br>strong | ..... | ..... | .... | 100 cc. | 2,000 cc. 5% dextrose in saline followed by shock | 100 cc. and B. P. to 106/55 in 15 mins. |
| 35 | 26 | Pelvic operation, large fibroleiomyoma | Mild | 74/55<br>80/60<br>90/60<br>90/60 | 130<br>124<br>112<br>104 | .....<br>1.0503<br>1.0491<br>1.0593 | .....<br>1.0251<br>1.0243<br>1.0234 | ....<br>36%<br><br>35% | 100 cc. | 500 cc. blood after shock controlled | Mild shock, after operation, controlled although highest B. P. 90/60, P. 112; then blood given; R. B. C. 4,000,000 to 4,110,000 |
| 36 | 25 | Multiple rib resection with blood loss | Mild | 80/50<br>104/60 | 125<br>96 | 1.0578<br>1.0534 | 1.0338<br>1.0264 | 40%<br>40% | 100 cc. | 500 cc. blood | During operation pulse weakened and B. P. dropped; this was checked with 50 cc. plasma and 500 cc. blood; later B. P. 80/50 and 94/46; 50 cc. caused prompt rise to 104/60, where it remained |
| 37 | 58 | Partial gastrectomy | Mild | 90/60<br>116/80 | 160<br>120 | 1.0542<br>1.0517 | .....<br>..... | ....<br>38% | 175 cc. | 1,000 cc. 5% dextrose in saline | 60 cc. before operation, 55 cc. to control shock; 60 cc. terminally, R. B. C. 4,000,000 to 3,600,000 |
| 38 | 46 | Partial gastrectomy | Mild | 88/64<br>120/80 | 130<br>90 | 1.0525 | 1.0241 | 39% | 110 cc. | 500 cc. blood and 200 cc. saline | Moderate lowering of B. P. and weakening of pulse during operation and 60 cc. given; later B. P. 88/64; 50 cc. and blood elevated it to 120/80 |
| 39 | 45 | Chronic blood loss and severe anemia, multiple fibroleiomyomas | Mild | 90/42<br>90/42 | 120<br>120 | ..... | ..... | .... | 60 cc. | ..... | Bleeding freely, very weak, pale, restless; known pyrogen containing water inadvertently used; patient had reaction |
| 40 | 18 | Left thigh amputation for osteogenic sarcoma | Mild | .....<br>112/70 | 156 weak<br>148 strong | ..... | ..... | .... | 100 cc. | 1,000 cc. 5% dextrose followed by shock | Patient cold, pale, profuse perspiration, weak pulse; noticeable improvement after 60 cc. and B. P. 112/70, 10 mins. later |
| 41 | 11 | Gunshot wound of foot | Mild | ..... | Weak, fast | ..... | ..... | .... | 75 cc. | 1,000 cc. 5% dextrose in saline | Described as being in shock with improvement after 75 cc. |
| 42 | 68 | Colostomy | Mild | 88/72<br>104/74<br>85/60 | 160<br>160<br>130 | ..... | ..... | .... | 100 cc. | ..... | Fast weak pulse, profuse sweating, declining B. P.; 100 cc. and B. P. 104/74 in 5 mins.; back to 98/74 5 mins. later, and sustained in that range |
| 43 | 26 | Abdominal pregnancy with severe hemorrhage | Severe | Imperceptible<br>65/50<br><br>100/60<br>Imperceptible<br>70/35<br>120/80 | Imperceptible<br>Just palpable<br>94<br>Imperceptible<br>160<br>112 | .....<br><br>.....<br><br>.....<br>..... | .....<br><br>.....<br><br>.....<br>..... | 39%<br>9.8G<br><br>23%<br>8.85G<br><br>7.2G<br>11.1G | 400 cc. | 4,000 cc. whole blood and 1,500 cc. saline, 50 cc. 50% dextrose solution | Estimated blood loss was 2,500 to 3,000 cc.; primary rise to 65/50 in 5 mins. with 130 cc.; in next 45 mins. 60 cc. plus 50 cc. 50% dextrose given and B. P. to 100/60; B. P. drop probably due to hemoglobin at critical level; 210 cc. elevated B. P. to 70/35; then 4,000 cc. blood and B. P. steadily to 120/80 and sustained |
| 44 | 19 | Traumatic injuries of face | Mild | 90/40<br>110/70 | 64 weak<br>68 strong | ..... | ..... | .... | 50 cc. | ..... | Patient cold, pale, sweating and mentally dull; 50 cc. and B. P. immediately to 110/70, sweating ceased, patient began talking rationally |
| 45 | 25 | Ruptured tubal pregnancy | Mild | 74/60<br>126/70 | 96 weak<br>Strong | ..... | ..... | .... | 100 cc. | ..... | Cold, pale, respiration shallow, pulse weak, slightly cyanotic; 100 cc., B. P. to 126/70 in 35 mins., markedly improved |

corresponding to cases in the former group. It should be understood that analysis of results in this series of 45 cases refers to control of shock and is not directly concerned with basic pathologic changes or ultimate outcome of surgical conditions. It is also agreed that some of the patients in mild and moderate shock would no doubt have responded to less effective measures alone. Nevertheless, because of the element of uncertainty in any case of shock, the most efficient available therapy should always be employed.

Where hemorrhage was a large or even a dominant factor in shock, concentrated plasma was found to be so effective and rapid in action that it was used not merely as a blood substitute but as a definite addition and improvement to the use of whole blood. Three cases of our series are reported in some detail to illustrate

the typical response to hypertonic plasma therapy. Case 1 is typical of the shock seen in hospital operative cases, case 3 illustrates the treatment of shock when the hemoglobin content approaches the critical level, and case 16 is due principally to exsanguinating hemorrhage.

CASE 1.—A white woman aged 46 passed into profound shock shortly after a vaginal hysterectomy. At operation the anesthetic was considered satisfactory and no excessive blood loss was noted. She was cold and clammy, sweating profusely and tossing restlessly. The heart tones were faint and weak, while the blood pressure and pulse were imperceptible in either arm. In view of her grave condition 100 cc. of hypertonic (four times) plasma was given intravenously in one minute. The sweating diminished and the patient improved, but since the pulse and blood pressure could not be obtained an additional 100 cc. of the plasma was rapidly given five minutes later. Immediately the radial pulse became palpable and perspiration ceased. The rapid rise in blood pressure to 92 systolic and 84 diastolic at ten minutes, and 102 systolic and 78 diastolic at one hour is seen in chart 1. The pulse simultaneously improved to 112 and then 104 at one hour. The shock was considered under control and at this time 500 cc. of citrated blood was started intravenously because of a lowered hemoglobin. Satisfactory progress continued thereafter.

CASE 3.—A Negro woman aged 32, a multipara, quintigravida, gave a history of hypertension of two years' standing with recent headaches and convulsive equivalents. The blood pressure was 200 systolic and 130 diastolic on admission. The possibility of a toxemic factor was considered and in two stages the patient was bled 1,000 cc. and given 150 cc. of hypertonic (four times concentrated) plasma. There was no improvement, and a cesarean section was performed. During the operation there was considerable loss of blood followed by deep shock with imperceptible blood pressure in the arms. One hundred cc. of five times concentrated plasma was given rapidly, and in fifteen minutes the blood pressure was 130 systolic and 100 diastolic. However, it gradually decreased and in thirty minutes it was imperceptible. Then 100 cc. of four times concentrated plasma was repeated and the blood pressure in five minutes was 70 systolic and 60 diastolic, in ten minutes 80 systolic and 66 diastolic, but soon dropped to 66 systolic and 58 diastolic. It was assumed that the total circulating hemoglobin content had approached or reached the critical level, and 1,000 cc. of whole blood was given by two portals. Recovery from shock was rapid, as illustrated by chart 2, and three hours after the operation the blood pressure was 130 systolic and 100 diastolic.

CASE 16.—A white man aged 55 was admitted to the emergency service in profound shock. He had been found in a pool of blood following multiple lacerations of the neck. On admission he was comatose, cold, cyanotic, clammy and sweating profusely. The respirations were irregular and gasping, and the pulse and blood pressure could not be obtained. It was impossible to obtain a drop of blood from the fingertip. Shortly after admission 100 cc. of concentrated plasma was rapidly given intravenously. During the administration of the last 50 cc. the patient began to move and mumble. Sweating ceased abruptly. Within fifteen minutes the pulse was palpable and the patient, though irrational, was talking. A second dose of 50 cc. was given thirty minutes after the first, and 500 cc. of citrated blood from the bank was started intravenously. A third dose of 50 cc. of plasma was given when about 200 cc. of blood had been administered. Chart 3 shows the steady rise in blood pressure of 70 systolic and 50 diastolic at five minutes to 84 systolic and 54 diastolic at one hour. One hour and twenty minutes after the third dose, the blood pressure was 110 systolic and 70 diastolic and the pulse was 100. The following day an emergency tracheotomy was followed by a dose of 50 cc. of four times concentrated plasma with a rise in blood pressure to 90 systolic and 50 diastolic. From then on improvement continued and the patient was discharged recovered.

## COMMENT

As illustrated in the cases of shock herein reported, the effect of hypertonic plasma on shock is, in general, an almost invariable, immediate, marked and sustained increase in blood pressure. Other shock phenomena also show dramatic changes. Sweating, for example, may cease entirely before all of a dose of plasma is given, while return to consciousness from coma often occurs in a few minutes.

While there is some reason to believe that the extreme speed of response may be due in part to direct stimulation of the vascular system, there is also direct laboratory evidence of a remarkably early increase in circulating volume. The decrease in whole blood specific gravity, hematocrit, red cell count and hemoglobin content indicate a definite increase in plasma volume. That this increase in volume is due in large measure to withdrawal of tissue fluid into the circulation and not merely to the added volume of concentrated plasma is shown by (*a*) decrease of whole blood specific gravity, although the specific gravity of the added concentrated plasma was much greater than that of whole blood, (*b*) relatively little change in the specific gravity of the patient's plasma, occasionally a decrease, and (*c*) extent of the change in plasma volume, as shown by hematocrit or hemoglobin being out of proportion to the amount given. These evidences of increased plasma volume and fluid shifts can be found early, in fact immediately after the administration of plasma is completed.

This extreme speed of fluid shift is important in view of the rapidity with which large quantities of protein can be introduced into the circulation. The total effects of these changes are diametrically opposed to the mechanism of traumatic shock with its loss of plasma volume into the tissues. It is important to note that the easily utilized interstitial fluid according to Blalock [2] amounts to approximately three times the total volume of blood plasma in a normally hydrated person. This indicates that this source of fluid should be adequate except in severely dehydrated patients.

Another point is brought out by Brennan [17] in his demonstration that in shock red cells apparently take up water, increasing as much as 50 per cent in size. Hypertonic plasma should be superior to whole plasma in reducing erythrocyte size by water shift. Removal of fluid from abnormal locations seems preferable to mere addition of fluid to the circulation, since such misplaced fluid may be deleterious to capillary, tissue and red cell function. While critical statistical evaluation in clinical cases of this type is impossible, the definite impression is obtained that the scope of treatment of shock is extended to include cases otherwise unresponsive. In the treatment of severe posthemorrhagic shock, hypertonic plasma, followed by whole blood transfusion, has a definite place. As Blalock [2] has shown, transfusion of even greater amounts of blood than that lost by hemorrhage may not restore adequate circulation, particularly when the shock is severe and prolonged. In our clinical cases of this type there are indications that hypertonic plasma, by immediately accelerating the circulation, may yield beneficial results where whole blood alone might fail. We wish to emphasize that this stimulating effect seems to depend on the concentration and speed of administration possible by this type of plasma only. Consequently, even when unlimited quantities of blood are available, we recommend that hypertonic plasma be given.

When the loss of red cells reaches or exceeds the critical amount of 60 to 75 per cent lost, no amount of plasma alone will suffice and whole blood must be added for any permanent good result. However, with less

severe hemorrhage, concentrated plasma may be used as a blood substitute to good advantage. Put up in dry lyophilic form, accompanied with enough pyrogen-free water to make the four times concentrate, it has many points of superiority over whole plasma. For military use in particular, the smaller bulk, perfect storage, simplicity of giving by syringe, speed of administration and rapidity of therapeutic action recommend it.

Reactions have not been a serious problem in the Baylor University Hospital plasma service. Only three febrile reactions were encountered in two hundred and ninety-nine administrations of concentrated plasma, a reaction rate of only 1.003 per cent. In 1 case unsuitable pyrogenic water was added by mistake, and in the second instance the patient in hemolytic crisis was having chills and fever at irregular times. The third patient had a febrile reaction of the type caused by pyrogenic substances, although the specific error in technic was not found. In the entire series two transient urticarial reactions were seen. The low reaction rate is attributed to the use of strictly pyrogen-free water in preparing the concentrate, and to avoidance through proper desiccation of any possible denaturation of protein, deterioration in storage, precipitation of fibrin or failure of complete solution. Furthermore, no untoward effects from either increased potassium or sodium content due in part to concentration were ever observed.

A tendency toward carpopedal spasm was noted with massive doses in 2 children. One of these had previously had spontaneous spasm of this type. Intravenous calcium chloride immediately relieved this tendency, suggesting that the patient's ionic calcium might have been temporarily reduced, owing to union with the excess of sodium citrate in the plasma. For use in pediatrics, serum might therefore be preferred to plasma. In our experience with small amounts of serum there were no febrile reactions. We agree with Levinson [15] that in this respect it is immaterial whether serum or plasma is used.

Occasionally the patient complained of dull and vague aches along the course of veins receiving the plasma. This has invariably ceased after administration has been completed. Complaint was also registered when hypertonic plasma was inadvertently given into tissues, but the discomfort was of short duration and without after-effects.

Hypertonic plasma, like most potent therapeutic agents, can be somewhat dangerous if misused. Unless preliminary bleeding of more than four times the volume to be given is done, its use in congestive heart failure is definitely contraindicated. One instance of increased blood volume with pulmonary edema after plasma administration was encountered but was promptly relieved by phlebotomy. However, a small dose of concentrate after proper bleeding gives excellent results in pulmonary edema.

The doses of four times concentrated plasma used in our cases have frequently been larger than heretofore recommended. In shock the aim should be to supply at least 40 per cent of blood volume lost. This might require from 200 to 300 cc. for an average adult in deep shock. In actual use as little as 100 cc. usually suffices and may be repeated as required. However, since speed is important it is advisable in profound shock to give larger initial amounts of 150 to 200 cc. In hypoproteinemic states significant or dangerous increase of blood volume and raising of plasma protein levels following the administration of concentrated plasma may not occur because of the spongelike effect of depleted storage depots for plasma proteins. This rapid removal of plasma proteins, as described by Madden and Whipple,[9] has been observed in some cases. For example a dose of 200 cc. of four times concentrated plasma given in forty minutes to an edematous 48 pound (22 Kg.) child with nephrosis resulted in only transient and slight rise in blood pressure and an increase in plasma proteins not commensurate with the amount given. Subsequent large doses did raise and sustain these protein levels.

The use of laboratory tests in the study of early changes and course of shock was somewhat disappointing. This was true particularly when hemorrhage was a factor and hemoconcentration could not be used as a reliable criterion of shock. When hemoconcentration was definite and capillary changes were foremost in pathogenesis, these laboratory tests were of definite value in predicting and following blood volume changes. For this purpose we found the photoelectric hemoglobin estimation the most satisfactory of all the tests used.

### CONCLUSIONS

On the basis of clinical results in 45 closely followed cases of shock, intravenous hypertonic plasma is advocated as the treatment of choice in shock.

The safety of this form of therapy is reflected in the low febrile reaction rate of 1.003 per cent among 299 administrations of concentrated plasma.

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## *Clinical Notes, Suggestions and New Instruments*

### BACTEROIDES SEPTICEMIA

#### REPORT OF A CASE WITH RECOVERY

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Infections caused by bacteria of the genus Bacteroides, judged by our experience and by reports in the literature, are extremely rare, and, judged by the same criteria, cases of Bacteroides septicemia are still less frequently encountered. In a review by E. C. Rosenow Jr. and one of us [1] of 144 cases of septicemia with positive blood culture, exclusive of cases of subacute bacterial endocarditis associated with Streptococcus viridans, seen at the Mayo Clinic in the years 1934 to 1936 inclusive, Bacteroides was found to have been cultured from the blood stream in only 6 instances. In a later similar review by two of us [2] of 174 cases of septicemia with positive blood culture encountered in the three year period from 1937 to 1939 inclusive, Bacteroides was found as the causative organism in only 8 cases. In all of the foregoing instances as well as in 2 cases of Bacteroides septicemia reported by Thompson and Beaver [3] in 1932 the disease was fatal. Much credit must be given to the last mentioned authors for their stimulating studies and contributions on this subject, some of which were made in cooperation with Henthorne and Macy.[4] In 10 cases of Bacteroides with probable positive blood culture which Thompson and Beaver collected from the literature, recovery was

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1. Rosenow, E. C., Jr., and Brown, A. E.: Septicemia: A Review of Cases, 1934-1936, Inclusive, Proc. Staff Meet., Mayo Clin. **13**: 89-93 (Feb. 9) 1938.

2. Herrell, W. E., and Brown, A. E.: The Treatment of Septicemia: Results Before and Since the Advent of Sulfamido Compounds, J. A. M. A., to be published.

3. Thompson, Luther, and Beaver, D. C.: Bacteremia Due to Anaerobic Gram-Negative Organisms of the Genus Bacteroides, M. Clin. North America **15**: 1611-1626 (May) 1932.

4. Beaver, D. C.; Henthorne, J. C., and Macy, J. W.: Abscesses of the Liver Caused by Bacteroides Funduliformis, Arch. Path. **17**: 493-509 (April) 1934.

noted in only 4. In 6 cases of Bacteroides infection reported by Dixon and Deuterman[5] in 1937 in which the infection followed operation for carcinoma of the large intestine, recovery occurred in only one and a positive blood culture was not obtained in this instance.

The generic name Bacteroides was given by Castellani and Chambers[6] in 1919 to a group of bacteria which have been recorded by Bergey[7] as obligate, rod-shaped, non-spore forming anaerobes with variable motility and gram-staining characteristics. Henthorne, Thompson and Beaver[8] have described Bacteroides funduliformis and fragilis as the gram-negative organisms of the genus Bacteroides and mention the existence of Bacteroides ramosus as the gram-positive bacterium. According to these authors "strict anaerobes which may be classified in the genus Bacteroides have been isolated from fetid and gangrenous suppurations of practically all organ systems of the human being, as well as from normal mucous membranes." In our experience infections caused by Bacteroides have occurred principally as complicating factors in the wake of serious debilitating primary disease.

The case of Bacteroides septicemia which we are reporting at this time is the only one of this type at the Mayo Clinic in which we have known recovery to occur. In addition to the culturing of Bacteroides from the blood stream of the patient it was also identified in sputum resulting from a complicating pneumonia.

Cohen,[9] in a review of the literature and original research study in 1932, reported on the importance of anaerobic organisms in abscesses of the lungs. In the light of the development of distinct jaundice in this case it is of additional interest that Beaver, Henthorne and Macy have reported 2 cases of sepsis caused by Bacteroides funduliformis and associated with hepatic abscess. Henthorne and Macy with Thompson also have stressed the frequency with which abscesses of the lungs and joints are produced by Bacteroides.

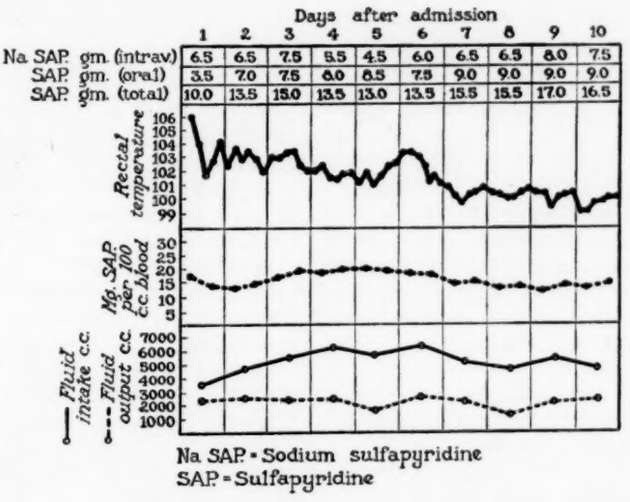
## REPORT OF CASE

A man aged 24 was admitted to the hospital in an extremely toxemic condition and with a temperature of 106 F. He stated that tonsillitis had developed a week previously and that three days later an attempt had been made to incise a supposed peritonsillar abscess on the right. Soon after this a temperature up to 106 F. developed. On examination a necrotic ulcer was noted in the right supratonsillar region, the right tonsil was swollen and the submaxillary and the subangular groups of cervical lymph nodes were swollen and tender. Palpation anterior to the border of the sternocleidomastoid muscle revealed that the internal jugular vein was exquisitely tender from the styloid process to the clavicle. A diagnosis of thrombophlebitis of the internal jugular vein with septicemia secondary to necrotic pharyngitis was made. The patient was given sulfanilamide on the supposition that the hemolytic streptococcus was the causative organism. Section and excision of the right internal jugular vein were considered but it was thought that the extremely critical condition of the patient contraindicated surgical intervention. At this time the urine contained albumin grade 2, casts grade 2 and erythrocytes grade 2 to 3 (on a grading basis of 1 to 4). Sulfanilamide 10.6 Gm. (159 grains) was given orally to the patient in the first thirty-six hours following admission and produced a concentration of 8 mg. of sulfanilamide per hundred cubic centimeters of blood.

Besides the complication in the throat, bilateral bronchopneumonia and jaundice developed three days after admission. On the fifth day after admission the serum bilirubin was 13.6 mg. per hundred cubic centimeters and the van den Bergh reaction was direct. The results of urinalysis persisted as previously noted.

The initial cultures which were made from the throat were negative for hemolytic streptococci, and cultures from the blood were also negative for these organisms at the end of forty-eight hours. We felt that on the basis of the foregoing observations it was quite possible that some other organism than the hemolytic streptococcus might be the cause of the existing infection and therefore we decided to use sulfapyridine in preference to sulfanilamide. This decision was based on the fact that sulfapyridine appears to possess greater therapeutic activity against a wider range of organisms than sulfanilamide possesses and is therefore the drug of choice in infections produced by unknown organisms and the additional fact that little or no clinical improvement had been produced by sulfanilamide. It is of interest and characteristic of cultures for Bacteroides that the blood culture which was negative at the end of forty-eight hours was positive for Bacteroides funduliformis at the end of eight days.

After the decision was made to use sulfapyridine in preference to sulfanilamide we immediately proceeded to establish and


Days after admission
1 2 3 4 5 6 7 8 9 10
Na. SAP. gm. (intrav) 6.5 6.5 7.5 8.5 4.5 6.0 6.5 6.5 8.0 7.5
SAP. gm. (oral) 3.5 7.0 7.5 6.0 8.5 7.5 9.0 9.0 9.0 9.0
SAP. gm. (total) 10.0 13.5 15.0 13.5 13.0 13.5 15.5 15.5 17.0 16.5
Rectal temperature
106 105 104 103 102 101 100 99
Mg. SAP. per 100 c.c. blood
30 25 20 15 10 5
Fluid intake c.c.
Fluid output c.c.
7000 6000 5000 4000 3000 2000 1000
Na SAP. = Sodium sulfapyridine
SAP. = Sulfapyridine

Course and treatment with sulfapyridine.

maintain a high concentration of sulfapyridine in the blood (from 16 to 18 mg. per hundred cubic centimeters) in accordance with our established plan for treatment of meningitis, septicemia and fulminant infections. The response to this type of treatment was immediate. Constant gradual improvement occurred in the patient's condition and the temperature by rectum declined from 106 to 100 F. at the end of eight days. By this time too the urine had returned to normal and no longer contained albumin, blood or casts. The jaundice gradually subsided and at the end of twenty-one days the level of the serum bilirubin had returned to normal. Improvement also was noted in the pneumonia, and the rectal temperature remained at about 100 F. until the thirtieth day after admission, when signs of pleurisy on the left side developed and the temperature gradually increased to reach 103 F. daily. On the thirty-second day culture of the sputum disclosed Bacteroides. The septic type of temperature persisted and after thoracentesis Dr. Harrington on the forty-seventh day performed an open operation with resection of the eighth and ninth ribs and evacuation of 2,000 cc. of pus from the left pleural cavity. The temperature returned to normal shortly after this procedure and remained normal thereafter.

The long schedule of treatment necessitated by the persistence of infection makes it advisable to summarize the therapeutic plan of procedure in order to conserve space. From the standpoint of chemotherapy it was necessary in order to obtain the desired concentration of 16 to 18 mg. of the drug in 100 cc.

5. Dixon, C. F., and Deuterman, J. L.: Postoperative Bacteroides Infection: Report of Six Cases, J. A. M. A. **108:** 181-185 (Jan. 16) 1937.

6. Castellani, Aldo, and Chambers, A. J.: Manual of Tropical Medicine, ed. 3, New York, William Wood & Co., 1919.

7. Bergey, D. H.: Bergey's Manual of Determinative Bacteriology: A Key for the Identification of Organisms of the Class Schizomycetes, Baltimore, Williams & Wilkins Company, 1934, pp. 404-413; 1939; pp. 556-570.

8. Henthorne, J. C.; Thompson, Luther, and Beaver, D. C.: Gram-Negative Bacilli of the Genus Bacteroides, J. Bact. **31:** 255-274 (March) 1936.

9. Cohen, John: The Bacteriology of Abscess of the Lung and Methods for Its Study, Arch. Surg. **24:** 171-188 (Feb.) 1932.

of blood to give from 6 to 9 Gm. (90 to 135 grains) of drug daily in six divided doses orally at intervals of four hours. Estimations were made each morning and evening of the concentration of sulfapyridine in the blood, and two supplementary doses of the sodium salt of sulfapyridine were given intravenously daily following the receipt of the reports from the laboratories in order to maintain the concentration that was desired. A total of from 4.5 to 7.5 Gm. (67½ to 112½ grains) of the sodium salt of sulfapyridine was thus given daily in addition to the oral dose of sulfapyridine, so that the total amount of sulfapyridine given in each twenty-four hours varied from 13 to 15.5 Gm. (195 to 232½ grains).

The plan of procedure for the first ten days of treatment is given in the chart.

The doses just cited served to maintain the concentration of sulfapyridine at between 14 and 19 mg. per hundred cubic centimeters of blood for the first eleven days of treatment; subsequently the concentration was decreased gradually to from 8 to 9 mg. per hundred cubic centimeters of blood and was maintained at this level during the remainder of the twenty-nine days of chemotherapy.

A total amount of 347 Gm. (5,205 grains) of sulfapyridine was given over a period of twenty-nine days and of this amount 230.5 Gm. (3,457½ grains) was given orally and 116.5 Gm. (1,747½ grains) of the sodium salt was given intravenously. These doses constitute the largest daily and total doses of sulfapyridine that we have ever used but were necessary in order to maintain the desired concentration of the drug in the blood because of the high daily level of intake and output of fluid. The patient was in an exceedingly toxemic state and he craved large amounts of fluid, so that, contrary to our usual plan of maintaining an approximate intake of 3,000 cc. of fluid and an output of 1,500 cc., in this instance no particular effort was made to limit fluids as long as it was possible to maintain the desired concentration of drug in the blood. In the light of our previous experience with septicemia and with Bacteroides septicemia in particular we believed that treatment was necessary as long as fever persisted and as long as the threat of the pulmonary or hepatic abscesses persisted in addition to the known complication of empyema. We also believed that this large intake of fluid possibly might be a vital factor in protecting the kidney from complications from the prolonged use of large amounts of sulfapyridine. The patient received oxygen therapy for his first two weeks in the hospital.

Aside from some tendency to mild anemia there was a comparative absence of toxic manifestations from the drug. Nausea and some abdominal distress were present at times late in the course of the treatment and we felt that these symptoms existed as manifestations of toxicity of the drug. The tendency to anemia was probably due in part to the use of sulfapyridine, but the sepsis was probably the most important factor in its production. We have always felt that it is advisable to use frequent small transfusions of blood in the presence of septicemia and that blood transfusions are also indicated when anemia is present in addition and when active chemotherapy is being carried on. Owing to the fact that the patient had an apparent inexhaustible supply of available blood from donor friends it was possible to give him an unusually large number of transfusions of blood. Transfusions averaging 300 cc. of blood were given daily for the first thirty-four days of treatment and a total of forty transfusions was given throughout the illness. Through the use of this measure the number of erythrocytes did not drop below 3,100,000 per cubic millimeter of blood and was generally maintained at about 4,000,000.

### COMMENT AND SUMMARY

This case represents the first instance of Bacteroides septicemia at the Mayo Clinic in which recovery is known to have occurred. One reason that this case is of particular interest is that sulfapyridine was administered. Heretofore, the sulfamido compounds have been considered not to be particularly effective against anaerobic organisms. Contrary to our usual experience, the infection was primary in nature and not superimposed on a chronic disease process.

Recovery occurred in spite of the fact that the Bacteroides septicemia was complicated by hepatitis and possibly liver abscess with jaundice; toxic, hemorrhagic, focal (?) nephritis; bilateral bronchopneumonia; left empyema, and cellulitis with thrombosis of the right internal jugular vein.

A total of 347 Gm. (5,205 grains) of sulfapyridine was given in twenty-nine days without the occurrence of serious toxic complications from the drug. Of the amount of sulfapyridine administered, 230.5 Gm. (3,457½ grains) was given orally and 116.5 Gm. (1,747½ grains) of the sodium salt was given intravenously.

This case illustrates well the principle that the important factor in treatment from the standpoint of chemotherapy is the maintenance of satisfactory concentrations of drug in the blood irrespective of the daily doses of drug necessary to maintain these desired concentrations.

Frequent transfusions and a high intake and output of fluid are undoubtedly factors of importance in the presence of septicemia in the prevention of complications when large doses of the sulfamido drugs are employed. We realize, of course, that in certain instances it may be advisable to give less fluid and therefore less drug than was given in this case in order to maintain the concentrations of drug desired in the blood.

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## DELAYED APPEARANCE OF REACTION TO ELASTIGLASS WRIST WATCH STRAP

W. W. BAUER, M.D., CHICAGO

A physician aged 48 with a history of autumnal hay fever since age 3 and gastric intestinal sensitivity to most of the cabbage family and attacks of severe headaches, sometimes of the migraine type, after the eating of cabbage and other vegetables in the same group, suffered a severe dermatitis from the wearing of a watch bracelet of the new synthetic, flexible, glass-like substance sold under various trade names. The onset of the symptoms was delayed two months after the purchase of the watch bracelet, although it was worn daily on the left wrist. The first manifestation was itching and erythema, followed in about twelve hours with typical urticarial wheals. These were found around the entire wrist except in the area under the watch itself. Although the first symptoms, itching and erythema, affected the entire area of skin with which the watch bracelet was in contact, the eruption at the end of twenty-four hours was in two definite lines, coinciding with the stitching of the bracelet. The stage of urticaria was followed in about forty-eight hours by extensive vesiculation with continuance of violent itching. The vesicles began subsiding at the end of five days without rupture, leaving an area of slighly raised induration. This area could be partially blanched on pressure or by putting the skin under slight tension, but even so there remained a definite evidence of inflammatory changes in the tissues.

On the appearance of the first symptoms, the watch was removed and placed on the other wrist for four hours to see what would happen. The same process was repeated on the other wrist to a somewhat more limited extent due probably to the shorter period of contact. On the right wrist there was less vesiculation but more induration.

The patient suffered in January 1940 from a generalized dermatitis attributed by a process of elimination to a newly purchased suit of cotton pajamas. Patch tests verified the etiologic significance of the pajamas. The patient also gave a history of having suffered a severe dermatitis involving both ankles immediately after the purchase and the first wearing of a new pair of socks.

The significant feature of this watch bracelet dermatitis is that sensitivity developed suddenly after the watch bracelet had been worn continuously for two months. The only significant precipitating factor which could be suggested is that dermatitis developed at a time when the patient spent four hours in conference in an excessively hot room and perspired rather freely.

535 North Dearborn Street.

## *Special Article*

# GLANDULAR PHYSIOLOGY AND THERAPY

## PHYSIOLOGY OF THE OVARIES

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NEW HAVEN, CONN.

*This special article is published under the auspices of the Council on Pharmacy and Chemistry. It is one of a series which will be published in book form as the second edition of "Glandular Physiology and Therapy." The opinions expressed in this article are those of the author and do not necessarily represent the official views of the Council.*—ED.

There are several important points about the ovaries which have emerged clearly under experimental attack. Once clearly defined, in many cases accentuated through experimental conditions, some of the phenomena stand out as normal in certain species but occur in others only occasionally. An instance is the formation of corpora lutea (accessory ones) in large follicles that have not ovulated. The ova are trapped inside, but the cells of the follicle take on luteal characteristics. Known for many years, this condition was first induced experimentally by unbalanced stimulation of the ovaries with anterior pituitary extracts.[1] It appears normally in the pregnant mare [2] and the pregnant porcupine [3] and occasionally in the nonpregnant monkey.[4] More careful observations may establish this as an occasional occurrence in women!

Another instance is the extreme development of the theca folliculi, the zone immediately surrounding the basement membrane about the outer layer of follicle cells, as described in the ovary of the pocket gopher by Mossman.[5] Although this tissue develops to a certain extent around growing follicles in the ovaries of most mammals, in the gopher it reaches extremes and apparently has an important secretory function accessory to that of the follicle, for it develops at puberty, when the symphysis pubis in this animal is resorbed to enlarge the birth canal. This resorption has been produced experimentally in males as well as in females, both gophers [6] and mice,[7] by injecting estrogen.

Another important point, which may now be mentioned as a fact rather than as an interesting possibility, is that a group of follicles, instead of just one, begins rapid growth which may result in ovulation of only one egg (or a few eggs in litter-bearing animals), the other follicles undergoing atresia and being resorbed. Loeb [8] emphasized this condition in his early studies of the guinea pig. It apparently needs the mass action of a group of follicles to assure ovulation of one (or a few), and this is apparently concerned with the secretory function of the follicles. The experiments of Hohlweg [9] and of Westman [10] are cited in this connection. Hohlweg reported precocious ovulation and the formation of corpus luteum following injections of estrogen in immature rats. Westman succeeded in destroying all of one ovary except one growing follicle. This was done in the rabbit by means of a fine diathermy needle. The other ovary was then removed. The lone remaining follicle was unable to proceed through normal development. If, however, a single dose of estrogen was given at the time of the operation, this lone follicle did develop normally and ovulate. Later this experiment was repeated in hypophysectomized animals.[11] This investigation assigns a supportive secretory function (estrogenic) to other follicles than the favored ones, i. e., to the ones which develop only partially, and then die and are eliminated. The "favored follicle" truly "stands upon the shoulders of its contemporaries."

In a similar way it may be inferred that the partly developing follicles probably secrete estrogen, which provides a necessary supporting action for the formation and function of corpora lutea. This, too, has been tested by injecting estrogen and found to be true.[12] In fact, injections of estrogen prevent the rapid involution of the corpora lutea which follows removal of both (1) the anterior lobe of the pituitary [13] and (2) the pregnant uterus with its embryos and placenta.[14] The latter evidence may mean that pituitary support of luteal function is partly through a stimulus to follicular production of estrogen rather than entirely through a specific "luteinizer." The support of luteal function by estrogen is in line with Willard Allen's observation [15] that progesterone and estrogen together were more effective in producing progestational changes in the uterus than was progesterone alone.

From the Department of Anatomy, Yale University School of Medicine.

Since the outline for the second edition includes "The Estrogenic Substance" by Dr. Doisy, "Corpus Luteum Hormone" by Dr. Corner, and "Menstruation" by Dr. Bartelmez, this chapter on "The Physiology of the Ovaries" is designed as general in nature. An attempt is made to reunite considerations of the production of both eggs and hormones. W. U. Gardner and C. A. Pfeiffer have contributed criticisms and suggestions for improvement. Limitations as to length prevent inclusion of several important aspects of ovarian physiology. Many additional references will be found in: Allen, E.; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, edition 2, 1939.

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This synergism seems to occur in both ovarian and uterine functions.

That such an influence may be felt more strongly locally than systemically, i. e., in the same ovary more than in the other ovary (to which the stimulus must be carried by the blood stream), is shown by Mossman's [3] description of conditions during pregnancy in the porcupine. The porcupine bears only one young at a time and therefore usually ovulates only one ovum. However, several other follicles succeed in reaching large size. When the favored follicle ovulates, these others are transformed into accessory corpora lutea, similar in all respects to the true corpus except that they have the ova trapped inside. So far this is similar to conditions in the pregnant mare [2] and to Corner's [4] observations in the ovaries of 4 of 23 nonpregnant monkeys killed between ovulation and the end of menstruation. But the remarkable thing about the porcupine is that as pregnancy progresses the accessory corpora in the ovary which ovulated, and therefore the one which contains the true corpus, persist throughout pregnancy, while those in the other ovary disintegrate before midgestation.[16] This might be explained on the basis of a strong hormonal influence establishing the luteinization but diminishing as gestation progresses until some local influence from the true corpus sustains structures in that ovary but fails to reach systemically to sustain those in the other ovary.

During recent years while the endocrinology of reproduction has been making such rapid advances,[17] there has been a tendency to discuss ovarian hormones apart from other phases of ovarian physiology. However, the production of eggs is still the primary function of the ovaries. Phylogenetically, this was the first ovarian function, and it is probably still the only function of the ovaries in some of the lower forms. The production of eggs in the mammalian ovary must involve slow but continuous shifting of transient structures of changing size—many follicles forming, growing and dying as a few mature, ovulate and are transformed into corpora lutea. The corpora in turn function for brief periods, depending to some extent on the fate of the eggs previously ovulated from the follicles that nurture them, before they shrink and disintegrate. Therefore, as far as egg production is concerned, the ovary might be compared to "a slowly boiling kettle" in which bubbles (follicles) are forming —from the surface, not from the bottom—sinking in as they grow to medium size, then reversing direction as they enlarge to rupture the surface at ovulation. But, as in any population, many follicles die before maturity; the mortality among ovarian eggs is very great.[18] In fact, this mortality is probably greater than formerly calculated, because new generations of eggs are differentiating from indifferent cells, during sexual maturity,[19] just as new sperm are continuously formed in the testes. This makes even more important the "selective elimination" to which growing eggs are subjected in the ovaries. These ova are eliminated not so much because they are defective as because there is only a limited supply of necessities, including anterior pituitary gonadotropic hormone, which is essential for their late growth. Many ova which would otherwise die can be brought to multiple ovulation by increased pituitary stimulation.[20] This is probably the key to the remarkable regenerative capacity of the ovary after removal of all but small parts [21] and to the compensatory hypertrophy of one ovary after removal of the other.

One important conclusion which follows is that the life span of ova in mammalian ovaries is usually a short one—in some of the small mammals it may be a matter of two or three weeks—almost as short as that of red blood corpuscles.[19b] This extensive development of transient structures involves constant rebuilding of the vascular nets of growing follicles and then further remodeling when these undergo atresia or ovulate to form corpora lutea.

To produce eggs in a majority of animals, especially birds, storage of nutriment seems necessary; therefore the ovaries must mobilize food for developing eggs. It seems probable that this must be done in competition with other bodily needs for nutriment in both growth and repair. In a general sense, this condition is reflected in the attainment of the major part of body growth before attainment of puberty presages mature ovarian function. Later during pregnancy in viviparous animals this competition for necessities between growing eggs in the ovary and bodily needs may be extended to include competition with the growing embryo and fetus, and during lactation, with function of the mammary glands. At first this competition is probably for things nutritional; later it may extend to include competition for extraovarian hormones, such as those of the anterior lobe of the pituitary, which are necessary for both body growth and reproductive function. This condition is accentuated by starvation, malnutrition or rapid growth of genital cancer. This sort of competition between organs or tissues must involve different rates of growth and metabolism, temporarily sustained.

The second function of the ovaries is the production of hormones. That this function is intimately tied up with growth processes is demonstrated by the striking growth of accessory genital organs of the female produced experimentally by injections of estrogen.[22] In fact, the sexual cycles, both estrous and menstrual, are fundamentally recurring waves of growth in the genital tract.[23] The ovarian estrogen is the essential hormone responsible for these cycles in nonpregnant females.[24] The luteal hormone is in a sense supplementary, acting apparently both as synergist and

16. In the pregnant mare the accessory corpora also do not persist throughout pregnancy.

17. Allen, Edgar; Danforth, C. H., and Doisy, E. A.: Sex and Internal Secretions, ed. 2, Baltimore, Williams & Wilkins Company, 1939.

18. Allen, Edgar; Kountz, W. B., and Francis, B. F.: Selective Elimination of Ova in the Adult Ovary, Am. J. Anat. **34**: 445 (Jan.) 1925.

19. (*a*) Allen, Edgar: Ovogenesis During Sexual Maturity, Am. J. Anat. **31**: 439 (May) 1923. (*b*) Evans, H. M., and Swezy, O.: Ovogenesis and the Normal Follicular Cycle in Adult Mammalia, in Memoirs of the University of California, Berkeley, Calif., University of California Press, 1931, vol. 9, p. 119. Evidence for ovogenesis is clearest in the adult mouse, in which, by use of the colchicine technic, hundreds of dividing cells, the first stage in ovogenesis, can be found at certain times in the estrous cycle (Allen, Edgar, and Creadick, R. N.: Ovogenesis During Sexual Maturity: The First Stage, Mitosis in the Germinal Epithelium, as shown by the Colchicine Technique, Anat. Rec. **69**: 191 [Sept.] 1937). Further search with improved technics will, I believe, furnish additional evidence in other mammals for this process, so fundamental in ovarian physiology.

20. Smith, P. E., and Engle, E. T.: Experimental Evidence Regarding the Rôle of the Anterior Pituitary in the Development and Regulation of the Genital System, Am. J. Anat. **40**: 159 (Nov.) 1927.

21. (*a*) Lipschütz, Alexander: On Some Fundamental Laws of Ovarian Dynamics, Biol. Rev. **2**: 263 (June) 1927. (*b*) Butcher, E. O.: Regeneration in Ligated Ovaries and Transplanted Ovarian Fragments of the White Rat (Mus Norvegicus Albinus), Anat. Rec. **54**: 87 (Sept.) 1932. (*c*) Van Wagenen, Gertrude, and Morse, A. H.: Personal communication to the author.

22. Allen, Edgar, and Doisy, E. A.: An Ovarian Hormone: Preliminary Report on Its Localization, Extraction and Partial Purification, and Action in Test Animals, J. A. M. A. **81**: 819 (Sept. 8) 1923.

23. Allen, Edgar; Doisy, E. A.; Francis, B. F.; Gibson, H. V.; Robertson, L. L.; Colgate, C. E.; Kountz, W. B., and Johnston, C. G.: The Hormone of the Ovarian Follicle: Its Localization and Action in Test Animals, and Additional Points Bearing upon the Internal Secretion of the Ovary, Am. J. Anat. **34**: 133 (Sept.) 1924.

24. Allen, Edgar: The Menstrual Cycle of the Monkey, Macacus Rhesus: Observations on Normal Animals, the Effects of Removal of the Ovaries and the Effects of Injections of Ovarian and Placental Extracts into the Spayed Animals, Contrib. Embryol., (no. 98), **19**: 1, 1927.

antagonist, with and against the estrogenic hormone, in various reactions. It is now definitely established that the androgenic hormones may also play important supplementary roles in ovarian endocrine function.[25] In fact, the secretion of the ovaries is probably a mixture of estrogens, androgens and progesterone, functioning at minimal levels during relatively quiescent phases of the sexual cycle but with successive generations of follicles and corpora periodically intensifying their function and momentarily modifying and dominating the total hormone output. The final result must depend on the degree of dominance for a while before the balance swings back. This principle apparently involves not only ovarian tissues but also their interactions with other endocrine glands.

Since the blood stream is the common carrier for both nutritional and hormonal supplies, the matter of competition for limited quantities of these substances, amounting actually to a struggle for survival in some instances, seems most fundamental in any concept of ovarian physiology. The developing eggs in the mammalian ovary might truly be considered a crowded population in a life and death struggle for limited amounts of vital necessities, a struggle so severe that only 400 human eggs, of hundreds of thousands, may reach maturity and be ovulated during the reproductive life of the average woman.

Recent thorough studies of the ovaries in the bat by Guthrie and Jeffers [26] give a clear picture of this sort of competition between growing follicles. During the month of September, in this species, all but one of a group of follicles are elminated as that favored one, "the follicle of ovulation," grows to ovulation size. The inhibition of follicular growth during pregnancy and lactation may also be logically explained by competition for necessary pituitary secretions during this time by dominant uterine and mammary functions. Interrelations of endocrine glands seem best interpreted by inclusion of a concept of balance through competitive utilization of certain limited vital necessities by successively dominant tissues or organs. The rapid growth of mammary cancer may suppress the function of other genital tissues for the same reason.[26a]

The concept seems to take concrete form more readily when the ovary is considered an aggregate, or colony, of transient individuals. As an ontogenic beginning, the primordial germ cells migrate to the genital ridge from the "germ cell crescent" of the embryonic disk of the bird [27] or from the endoderm of the gut of the mammal.[28] If this germ cell migration is successful, the genital ridge differentiates into an ovary or a testis; if the "germ cells" are prevented from reaching the ridge, a "sterile ovary" without ova (or an atypical testis) results and the primordial germ cells fail in establishing themselves as such in other sites.[29] Therefore both the immigrant cells and the genital ridge environment are important in the differentiation of the ovary.[30]

Apparently these primordial immigrants are not the ancestors of the definitive ova, those which ovulate during adult life. However, because of their presence in the embryonic genital ridge, the overlying peritoneal cells divide, and daughter cells from these divisions differentiate into ova and migrate toward the massed primordial ova beneath. With them go sister cells, which become follicle cells—also from the germinal epithelium. The ova do not divide further; the follicle cells do, and as they proliferate they group around the eggs to form the small follicles. Many such groups are formed during embryonic life, but these follicles and their contained ova probably all die and are resorbed before sexual maturity. New generations of ova are added to replace them,[31] the new growth continuing into adult reproductive life.[19a]

Therefore the hereditary characters, the chromosomes, of the eggs which are ovulated are probably not derived from the migrant primordial germ cells but are segregated in the peritoneum overlying the genital ridge. These cells have no chance to express their potentialities in the next generation unless the immigrant cells reach the site of the forming gonad and "beckon them in." This influence, this attraction, local in action, is probably in the nature of a secretion of the germ cells into the tissue fluids. It might be called a hormone if it were blood borne and its effects systemic. Since this influence probably moves by seepage through tissue fluids and is local, it is better classified as an "embryonic inductor" or "organizer." But hormones act similarly, as is shown in numerous endocrine experiments by more intense local than systemic actions.[32] This failure of the migrant primordial germ cells to become the immediate ancestors of the fertilized eggs that become our children does not mean a break in the chromosomal line of descent, for the undifferentiated cells of the germinal epithelium of the ovary are also descended from the same fertilized ovum. It is rather a temporary recognition of cousins while cells of the "true line" remain temporarily in undifferentiated obscurity.

Although the initial impulse of differentiation of sex in the embryo is undoubtedly genetic,[33] and the chromosomes of the primordial germ cells undoubtedly carry the determination of the genital ridge into the ovary or the testis, the further course of sexual differentiation, that of the accessory reproductive organs, seems to be taken over as an endocrine function of the developing gonad. There is evidence that in the female this embryonic ovarian hormone is estrogenic. At this time it is probably produced primarily by the partially growing follicles, for as yet interstitial and thecal tissues are scarcely developed at all, and corpus luteum participation is still far in the future.

Further development of the ovary consists of several successive "showers" or proliferations of cells, either in cords or in discrete masses, to form ova and follicle cells, and perhaps others which are not organized into follicles and which become interstitial cells. One of the earlier "showers," which forms the medulla of the ovary, seems to carry potentialities for testis formation under certain conditions. Later "showers" give rise to the cells of the fetal ovarian cortex. Thus

25. Koch, F. C.: Biochemistry of Androgens, in Allen, Danforth and Doisy,[17] chap. 12.
26. Guthrie, M. J., and Jeffers, K. R.: Growth of Follicles in the Ovaries of the Bat, Myotis Lucifugus Lucifugus, Anat. Rec. **71**: 477 (Aug.) 1938.
26a. Allen, E., Diddle, A. W., Strong, L. C., Burford, T. H., and Gardner, W. U. The Estrous Cycles of Mice During Growth of Spontaneous Mammary Tumors and the Effects of Ovarian Follicular and Anterior Pituitary Hormones, Am. J. Cancer **25**: 291, 1935.
27. Swift, C. H.: Origin and Early History of the Primordial Germ-Cells in the Chick, Am. J. Anat. **15**: 483, 1914.
28. Allen, B. M.: The Embryonic Development of the Ovary and Testis of the Mammals, Am. J. Anat. **3**: 89 (June) 1904.
29. Willier, B. H.: Experimentally Produced Sterile Gonads and the Problem of the Origin of Germ Cells in the Chick Embryo, Anat. Rec. **70**: 89 (Dec.) 1937.
30. Willier, B. H.: Embryonic Development of Sex, in Allen, Danforth and Doisy,[17] chap. 13.
31. Arai, Hayato: On the Postnatal Development of the Ovary (Albino Rat), with Especial Reference to the Number of Ova, Am. J. Anat. **27**: 405 (Sept.) 1920.
32. Lyons, W. R., and Templeton, H. J.: Intravaginal Assay of Urinary Estrin, Proc. Soc. Exper. Biol. & Med. **33**: 587 (Jan.) 1936.
33. Bridges, C. B.: Cytological and Genetic Basis of Sex, in Allen, Danforth and Doisy,[17] chap. 2.

the ovary has potentialities for both sexes.[34] It is now definitely known that ovarian tissue after puberty can secrete androgen under certain experimental conditions,[35] so that ovaries, as well as the adrenal cortex, may be an accessory source of masculinizing hormone in girls and women.

Apparently the genetic determination of sex involves a balance of genes in the chromosomes.[33] If the balance does not tip to a clear decision, sex intergrades may result. Apparently a similar balance exists between the androgenic and the estrogenic output of the gonads of both sexes. Sex intergrades have been produced by upsetting the usual endocrine balance.[36] Injections of androgens and estrogen early in embryonic life seem partly to reverse the sex as determined genetically or to block one potentiality and permit development in the direction of the opposite one. The transition of control by chromosomes to control by hormones needs much further study, but, since the convincing work of Stockard [37] on inheritance of endocrine imbalance in dogs and of Danforth [38] and Witschi [34] on factors determining type and color of plumage in birds, the significance of genic and endocrine dominance in influencing sex is clearly recognized.

When the consideration of embryonic life is extended to the mammal, ovarian hormones from the mother must be considered, for the placenta is by no means an absolute barrier against maternal hormones entering embryonic and fetal circulation.[39] Fortunately, sexual differentiation of the embryo one way or the other occurs fairly early in gestation. Although suppression of gonadal development by injecting hormones of the opposite sex has been accomplished in both directions, it usually must be done early, and higher levels of hormone must be attained than are found normally.[40]

There is now convincing evidence for the secretion of estrogen, progesterone and gonadotropins by placental tissues, and even by the chorion where no placenta is formed, as in the mare.[41] These products secreted during pregnancy are therefore predominantly fetal rather than maternal. In this connection the important point for ovarian physiology is that during pregnancy the endocrine function of the maternal ovaries is apparently "taken over" to a certain extent by the fetal membranes of the placenta. This is certainly true as far as the secretion of estrogen is concerned, for follicles seldom develop beyond the early antrum stage during pregnancy. In some animals, notably woman [42] and also the mare,[2] the true corpus luteum is no longer essential to the pregnancy after the first third of gestation.

A consideration of the physiology of the ovaries should include discussion of the growth of eggs, including storage of various kinds of yolk, the development and functions of egg membranes, both the fertilization membrane and the zona pellucida, the appearance of the corona radiata, the changes in the zona at the time of maturation and polar body formation, the withdrawal of processes of adjacent follicle cells from pores in the zona as the egg travels down the tube and the final dissolution of the zona in the uterus before implantation and increase in size of the segmenting ovum are possible—the latter being accomplished by shift of the hydrogen ion concentration of the uterine fluid to the acid side. Limitations of space exclude more than bare mention. Reference is made to the recent monograph of Pincus [43] for this phase of the subject.

One outstanding feature in the early growth of the ovum is its increase in size from deposition of yolk—the kind varying greatly with the species. In the pig there is much clear lipoid material; or there may be colorless yolk as in the rabbit, monkey or man, or pigmented yolk as in the carnivores. Yolk deposition in birds has been much studied. Precursors of definitive yolk can be stained cytologically by special dyes and their transport through (secretion by) the follicle cells demonstrated.[44]

As the ovum grows and cells multiply by mitotic division to form the follicle about it, all products of egg metabolism, both incoming and outgoing, must pass through these cells, because the blood supply lies beyond the follicular membrane (the basement membrane of the outer layer of follicle cells). At first, in the very small follicle, the limiting membranes between ovum and follicle cells and the basement membrane which separates follicular epithelium from stroma are hardly noticeable. As the follicle grows, they become much more prominent. The former becomes the tough, resistant capsule, the zona pellucida, through which processes from the inner layer of follicle cells extend to make contact with the surface of the ovum.

When the follicle of the mammalian ovary reaches a certain size, the liquor folliculi begins to form as an intercellular secretion. Cell-free liquor folliculi contains estrogen.[23] This is the best evidence that normally follicular cells secrete this hormone. The accumulation of follicular fluid is not necessary for secretion of estrogen, for solid granulosa cell tumors secrete this hormone.[45] The fact that other cells, such as theca, "interstitial" or even luteal cells, may also secrete estrogen does not invalidate this evidence but merely indicates that they also share this secretion. When ova are destroyed by carefully graded, critical doses of roentgen rays,[46] and regenerating nonovular tissue secretes estrogen, these experiments do not disprove

34. Witschi, Emil: Modification of Development of Sex in Lower Vertebrates and in Mammals, in Allen, Danforth and Doisy,[17] chap. 4.

35. Hill, R. T.: Ovaries Secrete Male Hormone: I. Restoration of the Castrate Type of Seminal Vesicle and Prostate Glands to Normal by Grafts of Ovaries in Mice, Endocrinology **21**: 495 (July) 1937.

36. Willier, B. H.; Gallagher, T. F., and Koch, F. C.: Sex-Modification in the Chick Embryo Resulting from Injections of Male and Female Hormones, Proc. Nat. Acad. Sc. **21**: 625, 1935. Burns, R. K.: The Effects of Crystalline Sex Hormones on Sex Differentiation in Amblystoma: I. Estrone, Anat. Rec. **71**: 447 (Aug.) 1938. Humphrey, R. R.: Studies on Sex Reversal in Amblystoma: III. Transformation of the Ovary of A. Tigrinum into a Functional Testis through the Influence of a Testis Resident in the Same Animal, J. Exper. Zool. **58**: 333, 1931.

37. Stockard, C. R.: The Physical Basis of Personality, New York, Norton & Company, 1931.

38. Danforth, C. H.: Relation of Genic and Endocrine Factors in Sex, in Allen, Danforth and Doisy,[17] chap. 6.

39. Courrier, R.: Nouvelles recherches sur la folliculine; contribution à l'étude du passage des hormones au travers du placenta, Compt.rend. Acad. d. sc. **179**: 2192, 1924.

40. Greene, R. R.; Burrill, M. W., and Ivy, A. C.: Experimental Intersexuality: the Production of Feminized Male Rats by Antenatal Treatment with Estrogens, Science **88**: 130 (Aug.) 1938; Experimental Intersexuality: The Paradoxical Effects of Estrogens on the Sexual Development of the Female Rat, Anat. Rec. **74**: 429 (Aug.) 1939; Experimental Intersexuality: The Effect of Antenatal Androgens on Sexual Development of Female Rats, Am. J. Anat. **65**: 415 (Nov.) 1939. Hamilton, J. B., and Gardner, W. U.: Effects in Female Young Born of Pregnant Rats Injected with Androgens, Proc. Soc. Exper. Biol. & Med. **37**: 570 (Dec.) 1937.

41. Newton, W. H.: Some Problems of Endocrine Function in Pregnancy, in Allen, Danforth and Doisy,[17] chap. 10.

42. Asdell, S. A.: Growth and Function of Corpus Luteum, Physiol. Rev. **8**: 313 (July) 1928.

43. Pincus, Gregory: The Eggs of Mammals, New York, Macmillan Company, 1936.

44. Guthrie, Mary J., and Jeffers, Katharine R.: A Cytological Study of the Ovaries of the Bats Myotis Lucifugus Lucifugus and Myotis Griscens, J. Morphol. **62**: 523, 1938.

45. Strong, L. C.; Gardner, W. U., and Hill, R. T.: Production of Estrogenic Hormone by a Transplantable Ovarian Carcinoma, Endocrinology **21**: 268, 1937.

46. Parkes, A. S.: On the Occurrence of the Oestrous Cycle after X-Ray Sterilization: I. Irradiation of Mice at Three Weeks Old, Proc. Roy. Soc., London, s. B **100**: 172, 1926; IV. Irradiation of the Adult During Pregnancy and Lactation; and General Summary, ibid. **102**: 51, 1927.

that follicles are normally the primary source of estrogen. They do prove that other tissues than follicles may undergo compensatory hypertrophy without follicular organization and retain this secretory function.

I think there is now evidence that all ovarian tissues may secrete estrogen—granulosa, theca, interstitial and luteal—but that follicular epithelium is probably normally the primary source. In the normal ovary the ova may be involved, for they are dynamic centers of the follicles. Primordial ova (without follicular appendages) may begin secretion of an "inductor." In birds the yolk contains estrogen.[47] The primary follicular fluid begins to form in partly developing follicles of mammalian ovaries, even after removal of the anterior lobe of the pituitary, as an intercellular secretion. The primary lakes of liquor folliculi first appear deep in the follicular epithelium. These follicles have very little theca, and the occurrence of interstitial cells is extremely variable in different species; therefore other possible sources do not exist at this time. Kingsbury[48] reported that interstitial cells are of variable and inconstant occurrence in ovaries of different species and are poorly developed before puberty even in the rabbit ovary, where later they are so conspicuous.

The changes in the follicle which precede ovulation, in fact, the changes which free the ovum from its attachment to the wall of the follicle and make its escape possible when the follicle ruptures, have been studied further in the rabbit by Pincus and Enzmann[49] and in the mouse by Snell and collaborators.[50] While the egg is still firmly attached by its cumulus to the follicle wall the nucleus is in resting condition.[51] When the ovum has become completely detached, the first maturation spindle has been completed and the first polar body formed. These phases of ovarian physiology would merit much more extensive discussion if limitations of space permitted.

The secretion of hormones by the ovaries is an ever expanding study. More than 40 estrogenic substances[52] have now been listed which act effectively in substituting for "the ovarian follicular hormone." Estradiol (dihydrotheelin) has been isolated from follicular contents and estrone (theelin) from sows' ovaries;[53] perhaps other estrogens are there. Freed and Soskin[54] postulated two estrogens with different properties from the ovaries of rats, one secreted by the granulosa and the other by the theca. Estrogens have been obtained from other than follicular sources: luteal tissue, ovaries without large follicles, and placental, chorionic and uterine tissues during pregnancy.[52]

Again there are several items of experimental evidence that show qualitative differences in the estrogenic content of tissues. For instance, luteal tissue from corpora of recent origin (corpora corresponding to eggs in the tubes) from human ovaries has a high estrogenic content.[55] In several other mammals estrogen is absent from luteal tissue or present only in traces. In working with fresh tissue from human ovaries (immediately after operative removal), demonstration of estrogenic response from liquor folliculi and from walls of follicles which contained normal ova is relatively easy.[56] When degenerating eggs indicated that large follicles were atretic, negative results were frequent.

It is much more difficult to demonstrate progesterone than estrogen in human corpora lutea, as seen from the experiments of Pratt, Hamblen, Kamm and McGinty.[57] From excision of corpora at operation, however, there exists much evidence that is as good as actual recovery of this hormone.[58]

There is experimental evidence that in some mammals progesterone may be secreted by the follicle during the few hours before ovulation. Little is known about the modification in cell metabolism that must occur as the follicular cells, and perhaps to some extent those from the theca, transform to luteal cells.[59] There seems no obvious reason to object to a concept that postulates the secretion of follicular and later luteal hormones by the same cells at different phases of a life cycle of secretory activity.

The dividing line between follicle and corpus luteum was formerly placed at ovulation. This will not hold for accessory corpora as described earlier in this paper. The name "corpus luteum" is misleading, for only old corpora are truly "yellow bodies." Surely during the early stages of development from the large follicles a gradual transformation is indicated. Also, evidence is now accumulating to show that the large follicle may begin to change its secretion, perhaps toward the luteal type, before ovulation. The finding in mouse ovaries of a set of "intermediate follicular-luteal structures,"[60] in which part of the wall was luteal and part follicular (the part near the egg), has a bearing on this transformation. One line of evidence for this comes from the work of Young and collaborators.[61] They studied mating reactions (receptivity) of ovariectomized female guinea pigs treated by injection of estrogen and progesterone and showed that while a certain percentage would experience estrous behavior when given injections of estrogen alone, nearly all would react if first "primed" with estrogen and then given injections of progesterone. This secretion of progesterone by the preovulation follicle might be associated with the secretion of the watery secondary liquor folliculi. This secondary liquor is easily distinguishable by fixation and staining reactions from the primary liquor, which forms more gradually before late preovulation enlargement of the follicle begins.[51] But if the large follicle secretes progesterone, which had formerly been considered a specific secretion of the corpus luteum, one more of those artificial dividing lines between follicle

47. Allen, Edgar; Whitsett, J. W.; Hardy, J. W., and Kneibert, F. L.: The Follicular Hormone of the Hen Ovary, Proc. Soc. Exper. Biol. & Med. **21**: 500 (May) 1924.

48. Kingsbury, B. F.: Atresia and Interstitial Cells of the Ovary, Am. J. Anat. **65**: 309 (Sept.) 1939.

49. Pincus, Gregory, and Enzmann, E. V.: The Growth, Maturation and Atresia of the Ovarian Eggs of the Rabbit, J. Morphol. **61**: 351, 1937.

50. Snell, G. D.; Fekete, Elizabeth; Hummel, Katharine P., and Law, L. W.: The Relation of Mating, Ovulation and the Estrous Smear in the House Mouse to Time of Day, Anat. Rec. **76**: 39 (Jan.) 1940.

51. Robinson, A.: The Formation, Rupture, and Closure of Ovarian Follicles in Ferrets and Ferret-Polecat Hybrids, and Some Associated Phenomena, Tr. Roy. Soc. Edinburgh **52**: 302, 1918.

52. Doisy, E. A.: Biochemistry of Estrogenic Compounds, in Allen, Danforth and Doisy,[17] chap. 13.

53. Westerfeld, W. W.; Thayer, S. A.; MacCorquodale, D. W., and Doisy, E. A.: The Ketonic Estrogen of Sow Ovaries, J. Biol. Chem. **126**: 181 (Nov.) 1938.

54. Freed, S. C., and Soskin, Samuel: Complete and Incomplete Estrogenic Hormones Arising from Different Sites in the Rat's Ovary, Endocrinology **21**: 599 (Sept.) 1937.

55. Allen, Edgar; Pratt, J. P.; Newell, Q. U., and Bland, L. J.: Hormone Content of Human Ovarian Tissues, Am. J. Physiol. **92**: 127 (Feb.) 1930.

56. Allen, Edgar: Human Ova from Large Follicles: Including a Search for Maturation Divisions and Observations on Atresia, Am. J. Anat. **46**: 1 (July) 1930.

57. Pratt, J. P.; Hamblen, E. C.; Kamm, O., and McGinty, D. A.: The Human Corpus Luteum and Progestin, Endocrinology **20**: 741 (Nov.) 1936.

58. Allen, Edgar; Hisaw, F. L., and Gardner, W. U., in Allen, Danforth and Doisy,[17] chap. 8.

59. Hartman, C. G.: Studies on Reproduction in the Monkey and Their Bearing on Gynecology and Anthropology, Endocrinology **25**: 670 (Nov.) 1939.

60. Allen, Edgar; Smith, G. M., and Gardner, W. U.: Growth of Ovaries and Genital Tract in Response to Hormones as Studied by the Colchicine Technique, Anat. Rec. **67** (supp. 3): 3, (March) 1937.

61. Young, W. C.; Dempsey, E. W.; Myers, H. I., and Hagquist, C. W.: The Ovarian Condition and Sexual Behavior in the Female Guinea Pig, Am. J. Anat. **63**: 457 (Nov.) 1938.

and corpus luteum used for the convenience of definition becomes less distinct.

The question of secretion of specific hormones by certain recognized tissues needs further discussion. Before the study of the distribution of estrogen in ovarian tissues was completed, the substance was isolated from the placenta,[62] and ovariectomy during early pregnancy[63] showed that the placenta elaborated, rather than stored, estrogen. Further evidence for the secretion of estrogens by the placenta comes from the continuation of estrogenic effects of placental origin when the embryos are killed while the placentas are retained; i. e. (1) the continued growth of the mammary glands, (2) the continued support of luteal function and (3) the continued regulation of water balance (retention) typical of pregnancy.[41]

One of the most outstanding features in ovarian physiology continues to be the remarkable domination of late follicular development and ovulation by the anterior lobe of the pituitary.[64] Apparently follicles can develop to fairly large size—to almost the full size of the ovum with several layers of follicle cells and the formation of small amounts of follicular fluid—without need for anterior pituitary stimulation. This is true in the rat after complete removal of the anterior lobe of the pituitary. However, further follicular development and ovulation and also the formation of corpus luteum require anterior pituitary stimulation.[65] If additional follicle-stimulating hormone is present, many more follicles develop than normally. This shows that limitation of this particular hormone is a normal condition.

Many measurements of ovarian ova of mammals have shown that before much fluid is secreted and accumulated in the follicle as liquor folliculi, the egg has reached its full size. Since this stage of follicular development is reached in hypophysectomized animals, the growth of the egg and early growth of the follicle are independent of anterior pituitary hormones. Pituitary stimulation undoubtedly plays a primary part in stimulating later secretion of liquor folliculi. It also may be involved in the maturation of the ovum just before ovulation and in ovulation itself; Pincus thinks that this effect is on the follicle cells rather than on the ovum, because the initiation of the first maturation division occurs in vitro simply on explantation of ovarian eggs from the follicles.[43]

Conditions at puberty which initiate cyclic sexual activity are extremely important. This undoubtedly involves interaction between the ovaries and the pituitary. It is probable that at the approach of adolescence estrogen from partly developing follicles influences the anterior lobe of the pituitary, at first stimulating, then depressing pituitary secretion of the follicle-stimulating hormone. Clark[66] reported the content of this hormone to be higher in the female than in the male rat at puberty, although later the male pituitary is more potent than that of the female. Frank[67] reported that low doses of estrogen stimulate, while high doses depress, pituitary gonadotropic function. The atresia of the majority of the group of large follicles would permit the increased secretion of the pituitary which is so vital for the late development of large follicles of the next generation. A succession of several partial (anovulatory) estrous or menstrual cycles which result from these ovarian pituitary relationships is the usual condition at adolescence of certain primates.[58] Puberty is usually not a sudden event but a gradual transition.[59] These conditions can be duplicated by injection experiments with estrogens. Several repetitions of a dose of estrogen subthreshold for an initial menstruation in the infantile monkey finally produce the first menstrual period.[68] Since effects of injected estrogens on the uterus itself appear to be transitory, the explanation probably must include interaction between ovarian estrogen and anterior pituitary gonadotropin.

Cystic follicles in the ovary have long worried the gynecologist. They are now easily produced experimentally by excessive or unbalanced stimulation with anterior pituitary gonadotropic extracts. In early stages of this condition a hyperestrogenic effect on the genital tract and mammary glands is usually present. Cystic follicles occur spontaneously in one genetic strain of rats,[69] which consequently remain for long periods in estrus (constant estrus rats), and Everett[70] has succeeded, by injections of progesterone, in inducing ovulation of these follicles.

Pfeiffer[71] has produced this condition of constant estrus by experimental modification of anterior pituitary gonadotropic function. One of the remarkable things about this experiment is that the effect is more than transitory; i. e., most endocrine effects disappear quickly after treatment with tropic substances is stopped, but in Pfeiffer's experiment altered anterior pituitary function continues after removal of the modifying factor. He transplanted testes from litter mates into 1 day old female mice. Since this was done in a closely inbred strain of mice, the grafted testes were vascularized and matured normally. The ovaries matured normally, and also the female accessory genital organs, but the animals were subject to "constant estrus," instead of "cyclic estrus," and did not recover from this condition even after the grafted testes were removed. Pfeiffer has explained these results as experimental modification by the testis grafts of the level or of the quality of anterior pituitary gonadotropic secretion. In rats similarly treated the injection of a pituitary extract containing the luteinizing principle induces ovulation; the animals mate and may become pregnant.[72] They often have difficulty in carrying pregnancy to term, but additional injections of the same extract make normal gestation and parturition possible.

The surgeon, confronted at laparotomy by cystic ovaries after symptoms of long duration, may think ovariectomy necessary, as it probably is in extreme cases. Experimental modification of anterior pituitary function, however, might remove the actual cause. Experiments of van Wagenen and Morse[73] point in this

62. Allen, Edgar; Pratt, J. P., and Doisy, E. A.: The Ovarian Follicular Hormone, J. A. M. A. **85**: 399 (Aug. 8) 1925.
63. Waldstein, E.: Frühkastration in der Schwangerschaft, Zentralbl. f. Gynäk. **53**: 1305 (May 25) 1929.
64. Zondek, Bernhard, and Aschheim, S.: Hypophysenvorderlappen und Ovarium. Beziehungen der endokrinen Drüsen zur Ovarialfunktion, Arch. f. Gynäk. **130**: 1, 1927. Smith and Engle.[20]
65. Smith, P. E., and White, W. E.: The Effect of Hypophysectomy on Ovulation and Corpus Luteum Formation in the Rabbit, J. A. M. A. **97**: 1861 (Dec. 19) 1931.
66. Clark, H. M.: A Prepubertal Reversal of the Sex Difference in the Gonadotropic Hormone Content of the Pituitary Gland of the Rat, Anat. Rec. **61**: 175, 1935; A Sex Difference in the Change in Potency of the Anterior Hypophysis Following Bilateral Castration in Newborn Rats, ibid. **61**: 193 (Jan.) 1935.
67. Frank, R. T.: The Sex Hormones; Their Physiologic Significance and Use in Practice, J. A. M. A. **114**: 1504 (April 20) 1940.
68. Allen, Edgar; Diddle, A. W.; Burford, T. H., and Gardner, W. U.: Ovarian Hormone Threshold for Experimental Menstruation in Monkeys, Am. J. Physiol. **117**: 381 (Nov.) 1936.
69. Everett, J. W.: Spontaneous Persistent Estrus in a Strain of Albino Rats, Endocrinology **25**: 123 (July) 1939.
70. Everett, J. W.: The Restoration of Cyclic Estrus and Ovulation in Persistent-Estrous Rats by Progesterone, Anat. Rec. **76** (supp. 2): 21 (Feb.) 1940.
71. Pfeiffer, C. A.: The Effects of an Experimentally Induced Endocrine Imbalance in Female Mice, Anat. Rec. **75**: 465, (Dec.) 1939.
72. Pfeiffer, C. A.: Maintenance of Pregnancy in Constant Oestrous Female Rats, Anat. Rec. **76** (supp. 2): 45 (Feb.) 1940.
73. Van Wagenen, Gertrude, and Morse, A. H.: Pregnancy Following Induced Cystic Changes in the Ovaries, Lancet **1**: 1220 (May 28) 1938.

direction. By long-continued injections of an anterior pituitary extract containing the gonadotropic principles they succeeded in producing in monkeys extremely cystic ovaries, demonstrated by laparotomy. Treatment was then withdrawn. Recovery of normal ovarian function was shown when animals later mated, carried normal pregnancies to birth at term and nursed their offspring.

Another instance of the dependence of ovarian function on anterior pituitary hormone is the trigger mechanism of ovulation in the rabbit (also in the cat and ferret). Stimulation of the cervix uteri affects the pituitary, apparently through a nerve pathway; pituitary secretion within the next few hours induces ovulation about ten hours later. The time cited was proved by removal of the anterior lobe of the pituitary, which, if left intact for one hour after mating, functioned sufficiently to induce ovulation.[74] Then cytologic evidence for this transient pituitary function was discovered by Friedgood and Dawson [75] in the existence of cells which react to special stains only during the few hours when this transient function exists.

Much work has been done in the last ten years on the physiology of ovulation itself. This began with the actual observation of ovulation by Walton and Hammond [76] in 1929. The process has since been photographed by moving pictures in several animals. While in the amphibia contraction of muscles in the wall of the follicle undoubtedly is of major force in ovulation,[77] in mammals increase in intrafollicular pressure is probably the dominant force. This is due to increase in secretion of the liquor folliculi, which forms rapidly in the preovulation follicle, and there is good evidence that this secretion is in response to pituitary stimulation. Events which directly precede ovulation include extreme stretching and "blowing out a pimple" in the weakest point of the follicle wall, a compression of the capillary net at this point, which leaves an avascular stigma, which finally breaks and through which follicular contents are extruded.[76] Before actual rupture of the follicle there may be a leakage of the more fluid follicular contents at this point, and then a rather sudden rupture and extrusion of the more viscous follicular contents, including the ovum with its cumulus of follicle cells still surrounding it.[78]

In some animals, notably the rabbit, the rupture of the follicle is accompanied by a remarkable change in electrical potential [79] as measured between the cervix and the symphysis pubis. In some other animals, which bear large litters, there may be a continued rise in electrical potential before ovulation with marked fluctuations in potential at the time the eggs are being ovulated,[80] but it may not be possible to associate a single rise in potential with the rupture of a specific follicle.[81]

Studies of changes in electrical potential have been made during the menstrual cycle in women.[82] In some instances the changes have been correlated with ovulation. At present it appears that alterations in potential, although occurring most frequently between successive periods, occur also at other times in the cycles in some women.[83] This indicates ovulation at other than the recognized usual time of ovulation in the cycle, or else the possibility that advanced development of follicles without ovulation may influence the rise in potentials.

Studies of the ovum and the follicles just preceding ovulation, especially those by Robinson and by Pincus, have greatly advanced the knowledge of the physiology of the ovary at this time. Reference is made to Pincus's book [43] for discussion of these stages.

During various phases of egg production, atresia, corpus luteum formation and retrogression, interstitial tissue appears. This is more abundant in some mammalian ovaries than in others; in some normal ovaries interstitial tissue may be very poorly developed or absent.[48] In broad definition interstitial tissue may include epithelioid cells between follicles or corpora, connective and vascular tissues being excluded. One source of formation of interstitial tissue is the proliferation of cells about a growing follicle to form the theca interna. This proliferation is readily gaged in normal ovaries by means of the drug colchicine, which shows proliferating follicles to have almost as many mitoses in the surrounding theca as among the granulosa cells of the follicles. Theca cells of growing follicles are really part of the follicle rather than "interstitial," but they become interstitial when atretic follicles undergo degeneration; in fact, Kingsbury stressed the principal derivation of interstitial cells in the ovary of the cat from thecal remains. As the follicle degenerates, the lipoid content of these cells increases. In this phase of its activity the theca of atretic follicles should not be confused with the theca of rapidly growing follicles as described by Mossman in the pocket gopher. Other interstitial cells may be derived by invaginations from the germinal epithelium, certain nests of cells or "anovular follicles," or possibly by cell multiplication in situ. The term "interstitial cells" as proposed by Bouin carries the inference of secretion. Accumulation of lipoids in these cells has been interpreted by Kingsbury [48] as storage rather than secretion.

There is now a considerable accumulation of experimental evidence that pituitary secretion is necessary for the proper formation and function of corpora lutea. Although the pituitary seems in these ways to dominate the ovaries, there is adequate evidence to show that the secretions of the ovaries react forcibly on the pituitary. The effects of ovariectomy in inducing castration changes in the pituitary, the prevention of these changes by injected estrogens,[84] the tumors of the pituitary following excessive estrogenic stimulation,[85] all point to the importance of the influence of ovarian secretions on the pituitary.

74. (*a*) Fee, A. R., and Parkes, A. S.: Studies on Ovulation: I. The Relation of the Anterior Pituitary to Ovulation in the Rabbit, J. Physiol **67**: 383 (July) 1929. (*b*) Deanesly, R.; Fee, A. R., and Parkes, A. S.: Studies on Ovulation: II. Effect of Hypophysectomy on Formation of the Corpus Luteum, J. Physiol. **70**: 38 (Aug.) 1930.

75. Friedgood, H. B., and Dawson, A. B.: Cytologic Evidence of the Gonadotropic Activity of the Rabbit's Anterior Hypophysis, Endocrinology **22**: 674 (June) 1938.

76. Walton, A., and Hammond, J.: Observations on Ovulation in the Rabbit, Brit. J. Exper. Biol. **6**: 190, 1928.

77. Rugh, R.: Ovulation in the Frog: II. Follicular Rupture to Fertilization, J. Exper. Zoöl. **71**: 163 (July) 1935.

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80. Rogers, P. V.: Electric Potentials in Normal Castrate, and Theelin Treated Rats, Proc. Soc. Exper. Biol. & Med. **35**: 257 (June) 1936.

81. Boling, J. L.; Barton, Dorothy S., and Burr, H. S.: Vaginal Electrical Correlates of the Estrous Cycle of the Rat, Anat. Rec. **76** (suppl. 2): 8 (Feb.) 1940.

82. Burr, H. S., and Musselman, L. K.: Bio-Electric Phenomena Associated with Menstruation, Yale J. Biol. & Med. **9**: 155 (Oct.) 1936. Rock, John; Reboul, Jean, and Wiggers, H. C.: The Detection and Measurement of the Electrical Concomitant of Human Ovulation by Use of the Vacuum-Tube Potentiometer, New England J. Med. **217**: 654 (Oct. 21) 1937.

83. Burr, H. S.; Musselman, L. K.; Barton, Dorothy S., and Kelly, Naomi B.: Bio-Electric Correlates of Human Ovulation, Yale J. Biol. & Med. **10**: 155 (Dec.) 1937.

84. Fevold, H. L.: Follicle Stimulating and Luteinizing Hormones of Anterior Pituitary in Allen, Danforth and Doisy,[17] chap. 17.

85. Cramer, W., and Horning, E. S.: Experimental Production by Oestrin of Pituitary Tumors with Hypopituitarism and of Mammary Cancer, Lancet **1**: 247 (Feb. 1) 1936. McEuen, C. S.; Selye, Hans, and Collip, J. B.: Some Effects of Prolonged Administration of Oestrin in Rats, ibid. **1**: 775 (April 4) 1936.

Ovarian function during pregnancy was first studied because of the importance of the corpus luteum to continued gestation. It has been known for a long time that the growth of follicles is inhibited during pregnancy (and also during lactation). With the recognition of the placenta (and of the chorion in case no true placenta is formed) as a source of estrogen in the pregnant animal, its function compensatory to the ovaries was indicated. First it was shown that removal of the anterior lobe of the pituitary after mating prevented the formation and function of the corpora lutea.[74a] Then injections of estrogen in hypophysectomized animals were known to prevent involution of the corpora. Recently Greep [14] has shown that if the pregnant uterus is removed from the rabbit on the tenth or fifteenth day of gestation, the corpora involute, and new follicles begin growth. If estrogen is injected into such animals, this involution of the corpora is prevented. However, Greep could not demonstrate estrogen in the rabbit placenta.

Snyder's [86] successful demonstration of stimulation of ovulation late in pregnancy, followed by superfetation, shows that follicular development is inhibited by deficiency of anterior pituitary hormone. He did this by injections of pregnancy urine in the rabbit late in gestation. This was one of the first experimental demonstrations of superfetation. This procedure usually prevented parturition.

A discussion of ovarian function would not be complete without citation of the evidence for secretion of androgen by the ovaries under certain conditions. It has been well established that androgens are excreted by females,[25] and at first the source was attributed to the adrenals, because of the masculinizing effects of tumors of the adrenal cortex. Hill [33] demonstrated clearly that ovarian tissue can, under certain conditions, secrete androgen. Using closely inbred strains of mice, he grafted ovaries in the ears of males. After the grafted ovaries had become vascularized, the testes were removed. In some cases, especially during a hot summer, the seminal vesicles and the prostate would undergo castrate atrophy; in others, especially during the winter, the accessory male organs were maintained in good functional condition. Hill [87] was then able to demonstrate an effect of temperature (the ovaries being implanted in the thin ears of the mouse were quickly subjected to environmental temperatures). When castrated males with ovaries grafted in their ears were living in warm temperatures, the seminal vesicles and prostates atrophied. When the same animals were removed to cool quarters, these accessory organs were maintained in functional condition, as shown by both organ weights and the appearance of intracellular secretory granules. After such proof one must consider the possibility of factors other than temperature modifying ovarian secretion from the estrogenic to the androgenic type—in fairly normal ovarian tissue as well as in the clearly pathologic arrhenoblastoma. Mere hypertrophy in the absence of a clearly demonstrable tumor might well be sufficient to account for varying degrees of masculinization in young girls.

Studies of changes in bones of birds [88] show formation of new spicules of cancellous bone in the marrow cavities at the time when eggs are ripening in the ovaries—and extreme conditions of a similar nature induced experimentally in both birds [89] and mammals (mice)[90] by injections of estrogens emphasize the importance of estrogenic ovarian hormone on calcium metabolism and bone structure. That a similar mechanism may be involved in the normal pneumatization of bones in birds is indicated in recent studies of the chick by Bremer,[91] who emphasized the similarity of the osseous changes preceding this invasion of the bones by the air sacs to the pathologic condition osteitis fibrosa.

At the same time at which new bone is replacing marrow in the long bones and even in the axial skeleton of the mouse under estrogenic stimulation, bone is being resorbed from the symphysis pubis,[90] as occurs in normal mice toward the end of pregnancy.

The profound effect of the seasonal variation in the length of daylight on ovarian function of some birds and a few seasonally breeding mammals has been established.[92] Increased egg laying in fowls through the winter from increased lighting is a commonplace in modern farming. Benoit's [93] work in the duck, which conclusively demonstrated the influence of a light stimulus through the eyes to the anterior lobe of the pituitary and thence on the gonads, furnishes concrete experimental evidence. The work of Kirschbaum and Pfeiffer [94] in sparrows, in which a differential response of ovaries and transplanted testes to light was demonstrated, carries the solution further. Recently it has been shown that the timing of ovarian function—follicular maturation and ovulation—can be reversed in nocturnal animals, e. g., the rat [95] and the mouse,[50] by reversing day and night light conditions.

The physiology of the ovary at and after the time of the menopause is an extremely interesting subject which can only be touched on in the present chapter. One thing which is certain is that ovulation usually stops at the menopause. This eliminates consideration of the endocrine function of newly forming corpora lutea after this time. The secretion of old corpora might persist for several months in diminishing amounts. However, even after the menopause follicles develop partly for several years. Follicles may also become cystic at this time. But as a generalization it might be said that usually internal secretion of the postmenopausal ovary is definitely declining. Concurrently there is an increase in the amount of the gonadotropic substance which appears in the urine.[96] The same is true of the premature menopause following ovariectomy.[97]

86. Snyder, F. F.: The Prolongation of Pregnancy and Complications of Parturition in the Rabbit Following Induction of Ovulation near Term, Bull. Johns Hopkins Hosp. **54**: 1 (Jan.) 1934.

87. Hill, R. T.: Ovaries Secrete Male Hormone: III. Temperature Control of Male Hormone Output by Grafted Ovaries, Endocrinology **21**: 633 (Sept.) 1937.

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90. Gardner, W. U., and Pfeiffer, C. A.: Skeletal Changes in Mice Receiving Estrogens, Proc. Soc. Exper. Biol. & Med. **37**: 678 (Jan.) 1938.

91. Bremer, J. L.: The Pneumatization of the Bones of the Chick and the Association Activity of Theelin, Anat. Rec. **76** (supp. 2): 9 (Feb.) 1940.

92. Bissonnette, T. H.: The Influence of Light upon Pituitary Activity, Proc. A. Research in Nerv. & Ment. Dis., Proc. (1936) **17**: 361, 1938.

93. Benoit, Jacques: Stimulation of the Hypophysis and Genital Glands in the Duck by Electric Light: Effect of Thyroidectomy on the Testis and Liver, Anat. Rec. **67** (supp. 1): 81, 1936.

94. Kirschbaum, A.; Pfeiffer, C. A; Van Heuverseyn, J. D., and Gardner, W. U.: Studies on Gonad-Hypophyseal Relationship and Cyclic Osseous Changes in the English Sparrow, Passer Domesticus L., Anat. Rec. **75**: 249 (Oct.) 1939.

95. Hemmingsen, A. M., and Krarup, N. B.: Rhythmic Diurnal Variations in the Oestrous Phenomena of the Rat and Their Susceptibility to Light and Dark, Copenhagen, Levin & Munksgaard.

96. Fluhmann, C. F.: The Endometrium in So-Called Idiopathic Uterine Hemorrhage, J. A. M. A. **93**: 1136 (Oct. 12) 1929.

97. Fluhmann, C. F.: The Significance of Anterior Pituitary Hormone in the Blood of Gynecologic Patients, Am. J. Obst. & Gynec. **20**: 1 (July) 1930; Anterior Pituitary Hormone in the Blood of Women: IV. A Preliminary Clinical Classification of Results in Non-Pregnant Individuals, Endocrinology **15**: 177, (May-June) 1931.

One point of extreme importance in the endocrine function of the postmenopausal ovary is the possibility of a shift toward secretion of androgen at this time. Masculinization phenomena and hypertrichosis occurring in a few women after the menopause require the inclusion of consideration of this possibility.

Ten years after the menopause the ovary is represented by a mere fibrous fold of tissue, very small and obviously not very important from the point of view of production of either eggs or hormones. Apparently ovarian function declines while the gonadotropic function of the pituitary is still efficient.

## *Council on Foods and Nutrition*

THE COUNCIL HAS AUTHORIZED PUBLICATION OF THE FOLLOWING REPORT.

FRANKLIN C. BING, Secretary.

### VITAMIN D MILK CONTAINING 600 U. S. P. UNITS OF VITAMIN D TO THE QUART IS NOT ELIGIBLE FOR LIST OF ACCEPTED FOODS

When vitamin D milk first was made commercially available, there were two general methods for its production. The irradiation method was capable of producing a milk containing at least 135 U. S. P. units of vitamin D to the quart. Recently there have been developed suitable methods of irradiating milk so that the resulting product contains at least 400 U. S. P. units of vitamin D to the quart. The vitamin D milk produced by the method of adding a vitamin D preparation, such as cod liver oil concentrate, has contained at least 400 U. S. P. units of vitamin D to the quart. The selection of this level of fortification at first was more or less fortuitous. At the time, now more than ten years ago, it was erroneously believed that one quart of such milk was equivalent to the vitamin D value of 3 teaspoons of cod liver oil, the then recommended daily dosage for infants. Subsequently it was learned that cod liver oil had a higher potency, and at present U. S. P. cod liver oil contains at least 85 units to the gram, or approximately 310 units to a theoretic teaspoon of 4 cc. This means that one quart of vitamin D milk containing 400 U. S. P. units of vitamin D is equivalent in vitamin D potency to one and one-third teaspoon of minimum strength U. S. P. cod liver oil to the quart. Even before the commercial production of these milks containing either 135 or 400 units of vitamin D to the quart, scientific and clinical evidence was obtained to show their nutritive value. A number of reviews of reports of these and subsequent studies have been published.[1] A paper by Jeans and Stearns [2] affords a discussion of recent available evidence on factors affecting vitamin D requirements. For the prevention of rickets, for good bone and tooth development and for excellent growth it appears that the vitamin D requirements of the full term artificially fed baby are satisfied if each quart of milk consumed contains between 300 and 400 U. S. P. units of vitamin D. Babies receiving human milk may require less vitamin D than babies receiving cow's milk. For children between infancy and adolescence, a daily allowance of 750 to 1,000 cc. (about 1½ to 2 pints) of milk containing from 300 to 400 U. S. P. units of vitamin D permits ample retention of calcium and phosphorus. For adolescents, data are not sufficiently numerous to permit an estimate of the quantity required, but there seems to be no reason why it should be less than the requirement of the baby. The requirements of adults for vitamin D are not known; during pregnancy and lactation the requirement is increased. A daily dosage of 800 units or more has been suggested for the lactating woman, together with an abundant intake of calcium and phosphorus.[2]

There now has been presented to the Council for consideration with a view to acceptance milk which has been fortified with 600 U. S. P. units of vitamin D to the quart. Except in the cases of some lactating women, evidence is meager that milk containing more than 400 U. S. P. units of vitamin D to the quart would have any nutritional advantages over milk containing but 400 U. S. P. units to the quart. For persons who need more than the amount of vitamin D which can be provided with suitable amounts of vitamin D milk containing 400 U. S. P. units of vitamin D to the quart, numerous other preparations can be prescribed, such as those described in New and Nonofficial Remedies.[3] Incidentally, it may be stated further that the Council believes preparations such as those described in N. N. R. are fully as effective, unit for unit, as vitamin D in the form of vitamin D milk, provided the concentration of vitamin D is not appreciably greater than 180 units to a gram of oil.

For the foregoing reasons, the Council has voted not to include for the present in the list of accepted foods any brands of milk for which claims are made that they contain more than 400 U. S. P. units of vitamin D to the quart. The evidence hitherto available suggesting the desirability of a higher amount of vitamin D in milk for protection from dental caries is not considered conclusive. Should evidence be developed to indicate that milk of higher potency is nutritionally desirable, the Council then will give further consideration to the acceptability of such products.

1. Jeans, P. C.: Vitamin D Milk, J. A. M. A. **106:** 2066 (June 13), 2150 (June 20) 1936. Report of the Council on Foods: The Present Status of Vitamin D Milk, ibid. **108:** 206 (Jan. 16) 1937. Report of the Council on Foods: Vitamin D Milk Produced by Feeding Cows Irradiated Yeast, ibid. **109:** 1814 (Nov. 27) 1937.

2. Jeans, P. C., and Stearns, Genevieve: The Human Requirement of Vitamin D, J. A. M. A. **111:** 703 (Aug. 20) 1938; in The Vitamins: A Symposium, Chicago, American Medical Association, 1939, chapter 26, p. 483.

### ACCEPTED FOODS

THE FOLLOWING ADDITIONAL FOODS HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON FOODS OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO ACCEPTED FOODS.

FRANKLIN C. BING, Secretary.

#### PREPARATIONS USED IN THE FEEDING OF INFANTS (*See* Accepted Foods, p. 156).

**H. J. Heinz Company, Pittsburgh.**

HEINZ BRAND CHOPPED CARROTS.

*Analysis* (submitted by manufacturer).—Moisture 93.1%, total solids 6.9%, ash 0.8%, fat (ether extract) 0.1%, protein (N × 6.25) 0.9%, crude fiber 0.7%, carbohydrates other than crude fiber (by difference) 4.4%, sucrose (Munson and Walker Method) 3.9%, calcium (Ca) 0.038%, phosphorus (P) 0.021%, iron (Fe) 0.0015%, copper (Cu) 0.00004%.

According to a report of biologic assay (1939) this product contains 4,000 international units of vitamin A, 12 international units of vitamin $B_1$ and 23 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 62 international units of vitamin C per hundred grams.

*Calories.*—0.22 per gram; 6 per ounce.

HEINZ BRAND CREAMED DICED VEGETABLES WITH CEREALS AND YEAST CONCENTRATE, a canned cooked mixture of milk, celery, carrots, white potatoes, tomatoes, onions, rice, sodium chloride, sugar, flour, and autolyzed yeast concentrate.

*Analysis* (submitted by manufacturer).—Moisture 86.1%, total solids 13.9%, ash 1.5%, fat (ether extract) 1.2%, protein (N × 6.25) 2.1%, crude fiber 0.3%, carbohydrates other than crude fiber (by difference) 8.8%, sucrose (Munson and Walker method) 2.5%, calcium (Ca) 0.099%, phosphorus (P) 0.061%, iron (Fe) 0.0012%, copper (Cu) 0.00011%.

According to report of biologic assay (1939) this product contains 1,150 international units of vitamin A, 7 international units of vitamin $B_1$ and 54 Sherman-Bourquin units of riboflavin per hundred grams. Report of chemical titration (1939) shows that the product contains 62 international units of vitamin C per hundred grams.

*Calories.*—0.54 per gram; 15 per ounce.

#### SUGARS AND SYRUPS (*See* Accepted Foods, 1939, p. 324).

**Bliss Syrup & Preserving Co., Kansas City, Mo.**

BLISS BRAND WAFFLE SYRUP, a mixture of corn syrup and cane sugar syrup, flavored with imitation maple flavoring.

*Analysis* (submitted by manufacturer).—Moisture 24%, total solids 76%, ash 0.3%, protein (N × 6.25) 0.7%, reducing sugars as dextrose before inversion 28.7%, total carbohydrate (by difference) 75%.

*Calories.*—3.0 per gram; 85 per ounce.

NECTAR BRAND WAFFLE SYRUP, same as Bliss Brand Waffle Syrup.

3. New and Nonofficial Remedies, Chicago, American Medical Association, 1940, p. 532.

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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SATURDAY, FEBRUARY 1, 1941

## HYGIENE IN AIR RAID SHELTERS

As a result of the vast numbers seeking the relative safety of air raid shelters in the London metropolitan area, many difficult and unexpected health and sanitary problems have arisen. At a meeting on this subject of the Section on Epidemiology and State Medicine at the Royal Society on Dec. 20, 1940, reported in the *British Medical Journal*,[1] many of the pressing questions on this subject were discussed, including ventilation, heating, the establishment of medical aid posts in the larger shelters, measures against liceborne disease, the provision of sanitary facilities, masking for the prevention of droplet infection, the use of insecticides, the disinfection of air and the problems of overcrowding. Two compensating factors were pointed out by Lord Horder: the stimulation of research which would undoubtedly lead to invaluable and permanent contributions to preventive medicine, and the opening up of a field for health education quite unparalleled in the past.

In the same issue of the *British Medical Journal* appear the further proposals of Lord Horder's Committee on Health in Air Raid Shelters[2] as presented to parliament by the Ministry of Health and the Ministry of Home Security. The committee recommended that arrangements be made to hospitalize those persons with "open" tuberculosis known to frequent shelters and further that each tuberculous family should have a family shelter. Compulsory powers to enforce these regulations are apparently already in effect.

The louse and other pests have necessitated serious thought. A short course of instruction for shelter wardens and a pamphlet giving briefly the life history of the louse, flea and bedbug and outlining simple measures for dealing with these pests are methods which have been evolved. Insecticides have been chosen and made available or have been ordered and further research has been begun. Compulsory powers have been established to delouse when necessary. The committee urged that the construction of shelter bunks and other fittings avoid as far as possible cracks, crevices and other harborages for insects. When shelters are found infested the committee suggested the adoption of a method of cleaning and scrubbing with soap and water containing cresol, together with the use of a painter's blow lamp to cracks and the like.

In the consideration of droplet infections and the preventive value of face masks, the committee recommended a cellulose acetate (cellophane) screen as the best for standard purposes. These have been ordered in quantity, but the committee did not object to certain other masks including the gauze type. From the evidence placed before it, the committee concluded that there were not sufficient grounds on which to recommend any of the reputed prophylactic measures such as medicated lozenges, gargles and throat sprays for use against infection in the shelters. It did not, however, advise against any of these measures for individual users of shelters. Smoking in public shelters should be avoided except when a separate compartment can be set aside. Finally, the committee is sponsoring certain controlled experiments with some of the newer forms of chemotherapeutic drugs used as nose and throat sprays under medical supervision.

At the discussion on December 20, Dr. P. G. Stock of the Ministry of Health stated that the shelter peak population of the underground tubes (subways) was reached in September at 186,000 but that it had fallen to about 100,000 at the time of the discussion. The hygienic problem in the tubes, however, constitutes only one aspect of the health problem in the shelters.

1. Hygiene in Air Raid Shelters, a discussion on Hygiene in Air Raid Shelters, Dr. J. Alison Glover presiding, Reports of Societies, Brit. M. J. **1**: 26 (Jan. 4) 1941.

2. Health in the Shelters, further recommendations by Lord Horder's committee, ibid. p. 24.

## THE CHIROPRACTIC THEORY OF LAW

Chiropractic is a distorted technic for the diagnosis and treatment of disease, which is being foisted on the American people, notwithstanding that its advocates lack the slightest conception, let alone appreciation, of the most elementary and clearly demonstrable facts in connection with the human body in health and disease. The realities of anatomy, pathology, physiology and chemistry mean nothing to chiropractors. Nevertheless, any informed person who points out the inanity of their theories and the baneful effects of their treatment is, by their propaganda, bigoted, hidebound, reactionary.

Chiropractors are in general quite uninformed in the field in which they hold themselves out as having some knowledge or aptitude. When they digress into other fields, they usually reveal such appalling ignorance that even the most casual observers see them in their true light. Few people realize that chiropractors, unlike

physicians, seldom if ever have any college education; indeed, some have not even completed the high school. In the *National Chiropractic News* for November-December 1940 appears an editorial entitled "Witch-Hunting in Indiana." This rumination was elicited in response to what appears to be a campaign of T. M. Overley, secretary of the Indianapolis Better Business Bureau, looking toward the prosecution under the laws of the state of Indiana of all unlicensed chiropractors practicing in the state. These individuals seek to practice in disregard of such an inconvenient and inconsequential technicality as obtaining a license after presenting to the Board of Registration in Medicine evidence of the educational qualifications required by the Medical Practice Act of Indiana and satisfactorily passing the examination required by law. Mr. Overley, so the editorial states, is "bluenosed" in this campaign "against qualified but unlicensed chiropractors." Were this statement not so pathetic, it would be ludicrous. "Qualified" by whom, for what? Shall cultists be permitted to ignore the applicable healing art licensing law if, in their own estimation, they possess the qualifications required by that law? Is the matter of licensure not a function of the state?

Quoting directly from the editorial:

> We asked him [the secretary of the Indianapolis Better Business Bureau] to distinguish and differentiate between the qualified, responsible [unlicensed] practitioner and the unqualified racketeer.

Granting, without admitting, that such a distinction could be drawn, the request for such a distinction itself evidences the unique mentality behind chiropractic thinking. Apparently it is good chiropractic theory to ignore a healing art licensing law, on the ground that such a law applies to the mass of men and to physicians but not to any adherent of this blissfully uninformed cult.

Mr. Overley, because of this campaign against all chiropractors violating the licensing laws of the state, because of his "purblind, bigoted" refusal to take the heat off "qualified but unlicensed chiropractors," is, the editorial remarks (after giving due credit to Gen. Hugh Johnson for originating the phrase), "suffering from halitosis of the intellect." This significant diagnosis, notwithstanding its origin in the General and its acceptance by the chiropractors, is just as scientific as chiropractic itself. The editorial implies that Mr. Overley's efforts to suppress the unlicensed practice of chiropractic must be bearing some fruit. However unfortunate from the chiropractic point of view, this consummation is distinctly in the public interest. Indeed, the public owes a debt of gratitude to Mr. Overley and the Better Business Bureau for their earnest campaign to make effective the medical practice act and for their self sacrifice in exposing themselves to the type of attack that such a campaign inevitably stimulates.

## THE RECORD OF A BLOOD DONOR

The value of human blood and plasma for transfusion in certain diseases is now well established; its lack of specific value for other conditions may not be so well known to physicians and to the public. The effects of the injection of nonspecific protein and of the materials contained in blood and plasma may be sufficient in themselves to develop nonspecific benefits which may cause false impressions of values. This exceedingly brief evaluation of blood transfusion is by way of introduction to a problem created by the drama associated with the donation of human blood for medical purposes. The creation of blood banks and serum centers, and the efforts now being made to secure donation of blood from hundreds of thousands of persons, will in time establish routines which may make such records as that which follows impossible.

In the *Cosmopolitan* magazine for November 1940 appeared an article relative to Mrs. Rose McMullin, who in 1935 apparently permitted herself to be infected with Staphylococcus aureus in order that she might develop antibodies. It had been decided to use her blood for transfusion in the case of her niece, who was suffering from an infection with Staphylococcus aureus. The physicians in the Hahnemann Hospital in Philadelphia, according to the article, utilized this procedure on her suggestion. They took blood from Mrs McMullin on several occasions and injected it into the niece. The niece recovered. Then in 1938, it is said, Mrs. McMullin responded to a request for blood to be used for a boy who was dying from Staphylococcus aureus infection in Delaware County, Pa. Some time later came an appeal from Chester, Pa., and again Mrs. McMullin responded. By this time apparently she began to be known as the "golden lady," probably because of the Staphylococcus aureus infection. She is also occasionally referred to as "the darling of the American Legion," since the American Legion is participating in the campaign to secure blood for transfusion for the military services.

According to the article in the *Cosmopolitan* magazine, "Mrs. McMullin had donated her magical help free, refusing the usual donor's fee. All she accepted was traveling expenses." Then Gabriel Heatter put Mrs. McMullin on his program. From that time requests for her blood began to come in great numbers, not only for cases of Staphylococcus aureus, but also for infections with Streptococcus viridans, from patients with leukemia and for other conditions. It would seem according to the article in the *Cosmopolitan* magazine, that Mrs. McMullin has a heavy file of letters of gratitude from physicians and that "she has given over 26,000 cubic centimeters of her golden life stream" [sic].

In the files in the headquarters office of the American Medical Association, information has accumulated which must be placed with that in the *Cosmopolitan*. First is a letter from a physician in Johns Hopkins Hospital who

inquired about the use of her blood for a case of myeloid leukemia. In this instance, the doctor writes, the parents of the child had been informed by Mrs. McMullin's agent that she had recovered from leukemia and that her blood contained the proper neutralizing bodies. It was stated that she would ask no fee but merely $500 for her expenses. References were given to two physicians who were said to have used her blood for cases of leukemia, but specific inquiry revealed that the blood had not been of the slightest use in these cases.

Another letter from a physician in Newark indicates that her blood was offered for a case of Streptococcus viridans infection, with a request for $300 to cover expenses. A third letter from a physician in Louisiana concerned a patient with subacute bacterial endocarditis. Next comes a report from a physician in New York, enclosing extended correspondence with Mrs. McMullin, begun because the father of a 6 year old girl with lymphogenous leukemia asked that a transfusion be made with the blood of Mrs. McMullin. An extended correspondence indicates that Mrs. McMullin did not insist that her blood would help a patient with leukemia but said she would take a while to build up her blood so that it could be used in that direction. In October 1940 her blood was examined by a New York physician, who found that she had a moderate anemia; he refused to use her blood until she could get a certificate from her own physician that it would be satisfactory.

Next comes a communication from a physician in Pennsylvania late in December. A farmer's boy in his community had Streptococcus viridans infection with subacute bacterial endocarditis. In this instance the Philadelphia *Inquirer,* having learned of the case, telephoned offering the services of Mrs. McMullin, who it seems was at that time in Oklahoma City giving her blood to another patient with Streptococcus viridans infection. The physician had difficulty locating Mrs. McMullin and after correspondence discovered that her blood was not of the right type. She was, however, apparently making a series of visits to various communities for the distribution of her blood. A physician from Missouri and another from Alabama who had experiences with Mrs. McMullin wrote that she states she will give her blood just for "expenses" but that her expense sheets "would make our national debt pale into pauper figures."

There comes also at this time a letter from a physician in Missouri who requested that Mrs. McMullin send her serum in a small bottle, having it taken by one of the blood banks in New York. The price asked for these bottles of serum was $100 per bottle. The amounts which came in these bottles varied from 210 to 51 cc. of serum.

In the case of one boy with streptococcic endocarditis, Mrs. McMullin provided enough blood for seven transfusions of approximately 200 cc. each over a period of two weeks. When the patient failed to respond, she insisted that the physician discontinue the sulfathiazole. This he did, but the fever went upward again immediately, so the sulfathiazole was again administered, whereupon there occurred an immediate drop in the temperature.

This is the record to date of a widely publicized blood donor. It provides many strange sociologic and psychologic facets. The report indicates the need for some type of control over this form of medical activity.

## *Current Comment*

### NEW TYPE OF VIRUS FROM EPIDEMIC INFLUENZA

In February and March 1940 an epidemic of acute respiratory disease simulating epidemic influenza occurred at Irvington House, a convalescent home for children with rheumatic heart disease. Reports of an investigation of this epidemic by Francis [1] indicate that neutralization tests done with serums obtained from early cases failed to reveal any rise in antibody titer against the standard PR8 strain of influenza virus. One of the ferrets inoculated with throat washings from one of the patients (Lee) developed some respiratory distress. At necropsy on the sixth day, mild bluish discoloration of the lower lobe of the left lung was disclosed. Other investigations indicated clearly, according to the criteria established in 1937 by Francis and his co-workers, that this outbreak of respiratory disease was not associated with the virus of influenza (PR8). However, the serums of Irvington House patients which had not exhibited a rise in convalescent titer against the standard PR8 strain were tested against a 10 per cent mouse lung suspension containing the new virus called the Lee virus. In short, the investigations definitely established the causal association of the Lee virus with the Irvington House epidemic and demonstrated a complete lack of serologic relationship between that virus and strains of virus isolated from other epidemics of influenza. Similar observations were made with regard to the January and February 1940 epidemic throughout the Southeastern portion of the United States. Clinically both epidemics were indistinguishable from mild epidemics caused by the PR8 strain. Of additional interest were the studies on the widespread epidemic of 1936. Serums—which had been kept in storage—from two patients typically involved in that epidemic were tested against both the PR8 and the Lee virus. Pronounced rises of titer against the Lee virus occurred but not against PR8. In consequence, this epidemic four years earlier was apparently also due to virus of the Lee type. These observations lead to important conclusions: the epidemics of 1936-1937 and 1938-1939 have been shown to be caused by influenza virus of the usual variety, while those of early 1936 and 1940 are of the Lee type. Clinically the two are indistinguishable but the two infections apparently present completely serologically

1. Francis, Thomas, Jr.: A New Type of Virus from Epidemic Influenza, Science **92**: 405 (Nov. 1) 1940.

distinct entities and independent cycles. Until further differential studies are made, however, they should both be considered epidemic influenza caused by virus of different serologic types. Following a classification recently suggested, the established form of epidemic influenza (caused by the PR8 virus) is classed influenza A, and outbreaks caused by virus of the Lee type are to be designated influenza B.

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## BLOOD PLASMA FOR GREAT BRITAIN

On Nov. 4, 1940 Dr. DeWitt Stetten,[1] chairman of the board of medical control and vice president of the board of trustees of the Blood Transfusion Betterment Association, reported to the committee on public health relations of the New York Academy of Medicine on the blood plasma for Great Britain project. The first meeting to consider this enterprise took place on June 12, 1940. The Red Cross agreed to advance $25,000 with an additional grant of $5,000 and to conduct the publicity necessary to obtain volunteer donors. The call for donors was made through the press, over the radio and by the wide distribution of descriptive posters and pamphlets. The response was immediate and enthusiastic. From August 15 to November 1, 6,961 volunteer donors were sent to the eight cooperating hospitals. To this number 404 were added by the hospitals themselves. Of this total of 7,365, 381, or 5.17 per cent, were rejected for various reasons. The blood of 75 donors (1.07 per cent) was rejected because of positive Wassermann tests for syphilis. Up to and including Nov. 1, 1940, 950 liters of plasma saline solution was released to the Red Cross as sterile and ready for shipment. Preference was given to plasma rather than to serum, and to liquid rather than to dried plasma. To date 30 liters, or 3.15 per cent, of the solution was lost because of contamination. By the first of November 747 liters of plasma saline solution was shipped abroad. The rule was adopted that the age of a donor must be over 21 and under 60 years, the minimum systolic blood pressure 110 and the hemoglobin 80 per cent. Blood with even the slightest positive test for syphilis is discarded. Fifty cc. of a 5 per cent solution of sodium citrate was added to 500 cc. of blood. A 1:10,000 solution of merthiolate is added for its bacteriostatic and bactericidal effect. To keep the plasma from becoming too viscous and to prevent the precipitation of fibrinogen, 50 per cent dilution with physiologic solution of sodium chloride is practiced. The 1 liter Baxter plasma-vac bottle was selected as container. The pooled plasma and the plasma saline solutions were kept until shipment at a temperature of from 3 to 5 C. Bacteriologic studies were first made at the various hospitals and were simultaneously checked at the laboratory of Dr. Frank Meleney by cultures made on the third, seventh and fourteenth days. Toxicity was determined by animal tests. The advisability of the conversion of the plasma into serum by precipitating out the fibrinogen with a calcium salt is now being considered. The success of the enterprise is due largely to the voluntary service on the part of various specialists in the field of blood transfusion, the doctors, the nurses and hospital personnel, all of whom offered their services gratuitously. The appointment on October 1 of Dr. Charles R. Drew, assistant professor of surgery at Howard University College of Medicine, as salaried medical supervisor was a wise step. A number of related problems are being investigated. One of them is the development of a satisfactory method of drying plasma or serum. This, Dr. Stetten believes, will be the eventual solution of the problem because of the much greater stability of the dried product, its smaller bulk, the relative simplicity of packing, storing and transporting it and the much lesser danger of loss from breakage. The importance of the development of a system of mass production of blood substitutes to our own defense program is evident.

1. Stetten, DeWitt: The Blood Plasma for Great Britain Project, Bull. New York Acad. Med. **17**: 27 (Jan.) 1941.

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## "CUTTING THE DOCTOR'S BILL TO FIT"

Physicians were cognizant of the problem of providing good medical service to the indigent and low income classes long before social reformers began to take the problem into politics. And the medical profession did something about it! Fred DeArmond, "Cutting the Doctor's Bill to Fit," in *Nation's Business* for November, is impressed by two different types of approach:

> Doctors try a new procedure on a guinea pig first. If it works, they use it on a patient.
>
> . . . Social reformers . . . experiment on the whole nation and, if there isn't too much revolt, they then test the procedure on a guinea pig.

Between 1932 and 1938 more than 200 county medical societies entered into agreements with relief authorities to provide medical care for the indigent. In twenty-six states, county medical societies cooperated with the Farm Security Administration in trying out plans to provide medical service to the low income classes. Not all of these plans were a success and physicians did not expect them to be. They were frankly experiments. Organized medicine also experimented with medical service bureaus through which the indigent were "filtered" to the proper source of medical service and which made arrangements for convenient postpayment plans. Some of these experiments failed, but something was learned from each of them. And the whole nation was not used as a guinea pig. In a number of states, prepayment plans are now being introduced on a statewide basis. Sometimes an enabling act of the state legislature has been required. The state plans are not all alike. Michigan, California and New York, where the plans have actually gone into operation, differ in a number of minor details. In Wisconsin several plans were tested. The state medical society in every case is watching not only its own plan but those of all other states engaged in such an experiment. Unlike many social reformers and critics, the medical profession will abandon any of the features of a plan that prove unsatisfactory or may adopt any more successful features from other states. One difficulty seems to be common to all these plans. The public is not particularly enthusiastic about prepayment for medical service. There is no evidence that the citizens of this country are yearning for any universal compulsory system.

# MEDICAL PREPAREDNESS

***In this section of The Journal each week will appear official notices by the Committee on Medical Preparedness of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medical preparedness, and such other information and announcements as will be useful to the medical profession.***

## SIX THOUSAND FIVE HUNDRED ARMY GENERAL HOSPITAL BEDS

Six large general hospitals providing a total of 6,500 beds which are being built by the army are expected to be ready for use March 1, the War Department has announced. The hospitals are to be located in Atlanta, Ga., Charleston, S. C., New Orleans, Fort Benjamin Harrison, Indiana, Santa Barbara, Calif., and Vancouver, Wash. The total cost will be $8,879,969. New hospital facilities have also been authorized for Fort Francis E. Warren, Wyoming, costing about $311,500, consisting of a cantonment type hospital of two hundred beds on a three hundred bed plan.

## EXAMINATION FOR COMMISSIONS IN NAVY MEDICAL CORPS

Applications for commissions as medical officers in the U. S. Navy are now being received in the Bureau of Medicine and Surgery, Navy Department, Washington, D. C. Examinations for entrance into the Medical Corps of the regular Navy will be held on May 12 to 15, inclusive, 1941, at all of the larger naval hospitals, including those at Chelsea (Boston), Mass., Brooklyn, Philadelphia, Portsmouth (Norfolk), Va., Great Lakes, Ill., Charleston, S. C., Pensacola, Fla., San Diego, Calif., Mare Island, Calif., Puget Sound (Bremerton), Wash., and at the Naval Medical Center, Washington, D. C. Successful candidates from this examination will receive their appointments approximately two months from the date of the examination.

Applicants are required to be citizens of the United States between 21 and 32 years of age at the time of appointment, graduates of a class A medical school, and to have completed at least one year of intern training in a hospital accredited for intern training by the Council on Medical Education and Hospitals of the American Medical Association. They are required to be physically qualified and to demonstrate their professional qualifications by written, oral and practical examinations embracing the subjects of general medicine, general surgery, obstetrics and gynecology, and preventive medicine and jurisprudence. The physical and professional examinations usually require from three to four days for completion.

Successful candidates are commissioned as assistant surgeons with the rank of lieutenant (junior grade) in the Medical Corps of the Navy. An officer of this rank receives compensation of $2,699 a year if he has no dependents and $3,158 a year if he has dependents.

A "Circular for the Information of Persons Desiring to Enter the Medical Corps of the United States Navy," including data pertaining to physical requirements, promotion and retirement, may be obtained by addressing a request to the Surgeon General of the Navy, Navy Department, Washington, D. C.

## NAVY PLACES RESEARCH UNIT ON ACTIVE DUTY

The assignment to active duty of all officers and enlisted personnel of Laboratory Research Unit No. 1 of the U. S. Naval Reserve, for the purpose of conducting intensive research on methods of improving the immunizing capacity of influenza virus vaccine, has been announced by Secretary of the Navy Knox. The University of California has offered the use of the laboratory facilities of the university's medical school at Berkeley for this research. Cooperation with the Rockefeller Foundation, which supports the Influenza Laboratory at that location, and the California State Department of Health, has been requested. Commander A. P. Krueger, M. C., U. S. N. R., head of the Department of Bacteriology of the University of California Medical School, organized this laboratory research unit and will be in charge of the project, assisted by Lieut. Robert A. Hicks, U. S. N. R., of Tucson, Ariz., and nine specially qualified hospital corpsmen of the Naval Reserve. In conducting this research, it is planned to investigate all types of influenza occurring in Naval and Marine Corps personnel throughout the entire service. Laboratory Research Unit No. 1 was organized in 1934.

## A SECOND FIELD ARMY LABORATORY

About February 10 a second field army laboratory will be set up at Fort Sam Houston, Texas, for training purposes similar to the army laboratory set up at the same station recently. It will be a semimobile unit consisting of a stationary central laboratory and three smaller mobile laboratories housed in trailers. The laboratory of this kind now in operation has forty-five enlisted men attached to it and, of the thirty privates and privates first class, eighteen hold specialists' ratings; there is a master sergeant who is a senior laboratory technician, three technical sergeants providing a senior laboratory technician for each mobile unit, three staff sergeants, seven sergeants and one first sergeant. Eleven officers are assigned to the laboratory. As yet no commanding officer has been assigned to the new unit.

## DR. PARRAN TO STUDY CIVILIAN DEFENSE PROBLEMS

Dr. Thomas A. Parran, Surgeon General, U. S. Public Health Service, Washington, D. C., will serve on a four man commission to study civilian defense problems in Britain. Dr. Parran sailed for London January 18, to remain abroad about one month. The commission will study, under orders from the War Department and the National Defense Advisory Commission, problems of health, transportation, utilities and child evacuation in a country under bombardment.

# ARMY RESERVE OFFICERS ORDERED TO ACTIVE DUTY

## WAR DEPARTMENT

The following additional medical reserve officers had been ordered to active duty by direction of the War Department, Washington, D. C., up to January 17:

BECK, Morton Sidney, 1st Lieut., Philadelphia.
FAIER, Samuel Z., 1st Lieut., Omaha.
HOLDER, Hall G., Captain, San Diego, Calif.
HUNTER, Robert Charles, 1st Lieut., Washington, D. C.
JORGENSEN, Philip Burnell, 1st Lieut., Mosinee, Wis.
MATLIN, Edwin, 1st Lieut., New York.
PELTON, Bernard Lynn, 1st Lieut., Toledo, Ohio.
SINGE, Donald Clemenz, Captain, Bethesda, Md.
SLOCUM, Donald Barclay, 1st Lieut., Eugene, Oregon.
SUTULA, Stanley Joseph, 1st Lieut., Washington, D. C.
WALDRON, John Francis, 1st Lieut., South Orange, N. J.
WHITAKER, Lawson Spires, 1st Lieut., Washington, D. C.
WOLFF, Herman, 1st Lieut., Lynchburg, Va.
ZUCKERMAN, Sidney N., 1st Lieut., San Francisco.

## FIRST CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty with the regular army by the Commanding General, First Corps Area, since January 10. The First Corps Area comprises the states of Maine, Vermont, New Hampshire, Rhode Island, Massachusetts and Connecticut.

ADLER, Hyman, 1st Lieut., Brooklyn, Fort McClellan, Ala.
BATTISTA, Vincent J., 1st Lieut., New York, Fort McClellan, Ala.
BIRNBAUM, Morris S., 1st Lieut., New York, Fort McClellan, Ala.
BOGEN, Ben, 1st Lieut., Brooklyn, Fort McClellan, Ala.
BURSEN, Earl P., 1st Lieut., Brooklyn, Fort Ontario, N. Y.
COHN, Samuel H., 1st Lieut., Hartford, Conn., Fort Benning, Ga.
COHN, Stanley H., 1st Lieut., Brooklyn, Fort Dix, N. J.
DALY, Joseph P., 1st Lieut., Long Island City, N. Y., Fort Hamilton, N. Y.
DANISH, Louis J., 1st Lieut., Hollis, L. I., N. Y., Fort McClellan, Ala.
DIAMOND, Bernard, 1st Lieut., Brooklyn, Camp Livingston, La.
ERNST, Carl C., 1st Lieut., Great Neck, N. Y., Camp Shelby, Miss.
ERTEL, Harry, 1st Lieut., Jackson Heights, N. Y., Fort McClellan, Ala.
FEIGENBAUM, Harry A., 1st Lieut., Brooklyn, Camp Edwards, Mass.
FINK, Benjamin, 1st Lieut., Brooklyn, Fort McClellan, Ala.
GAMSO, Rafael R., 1st Lieut., Brooklyn, Camp Livingston, La.
GARBER, Israel E., 1st Lieut., Mattapan, Mass., Carlisle Barracks, Pa.
GOODKIN, George, 1st Lieut., New York, Camp Livingston, La.
HAHN, Joseph G., 1st Lieut., Brooklyn, Fort Devons, Mass.
LaTAIF, C. George, 1st Lieut., New Milford, Conn., Carlisle Barracks, Pa.
MELLONE, John A., 1st Lieut., Bristol, R. I., Fort Ethan Allen, Vt.
SCHILLER, Israel A., Captain, Brooklyn, Induction Station, Manhattan, N. Y.
SMITH, Charles S., Major, New Haven, Conn., Fort Devens, Mass.

## SECOND CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Second Corps Area, up to January 17. The Second Corps Area comprises the states of New York, New Jersey and Delaware.

BLUMENTHAL, Basil, 1st Lieut., Washington, D. C., General Dispensary, U. S. Army, Baltimore.
BRADEN, Frank Robert, Jr., 1st Lieut., Coraopolis, Pa., Camp Blanding, Fla.
BUTTERMORE, Ralph Morgan, 1st Lieut., Pittsburgh, Pa., Fort Eustis, Va.
COCKERHAM, Howard Lea, Jr., 1st Lieut., Baltimore, Fort Belvoir, Va.
CORSELLO, Whitney Carl, 1st Lieut., Pittsburgh, Fort Benning, Ga.
FISH, Henry, 1st Lieut., Scranton, Pa., Camp Lee, Va.
HADDEN, Thomas Miles, 1st Lieut., Saltsburg, Pa., Camp Shelby, Miss.
HARBATER, Melvin I., 1st Lieut., Forest Hills, L. I., N. Y., Camp Upton, N. Y.
HEINBACH, Wilfred Frances, Jr., 1st Lieut., Reading, Pa., Indiantown Gap, Pa.
HIRSCH, Lucien, 1st Lieut., Brooklyn, Camp Livingston, La.
HOROWITZ, Alexander S., 1st Lieut., Jersey City, N. J., Camp Livingston, La.
HYMAN, Aaron, 1st Lieut., New York, Camp Livingston, La.
JURNOVE, Donald S., 1st Lieut., New York, Camp Livingston, La.
KARPEL, Saul, 1st Lieut., New York, Camp Livingston, La.
KLASSON, David H., 1st Lieut., Brooklyn, Camp Livingston, La.
KLOPP, John Benneville, Major, Chester, Pa., Headquarters Company, Washington, D. C.
KRENTZ, Benjamin E., 1st Lieut., New York, Camp Livingston, La.
LEVISON, David Julius, 1st Lieut., Pittsburgh, Camp Shelby, Miss.
MANFREDI, Joseph J., 1st Lieut., New York, Camp Livingston, La.
McMASTER, Gilbert Brown, 1st Lieut., Pittsburgh, Camp Blanding, Fla.
MILHOLLAND, Arthur Vincent, 1st Lieut., Baltimore, Fort Belvoir, Va.
NOVALIS, Nicholas A., 1st Lieut., Long Island City, N. Y., Camp Livingston, La.
PASSARELLI, Arthur Francis, 1st Lieut., Washington, D. C., Fort Story, Va.
PINCUS, Morris H., 1st Lieut., Brooklyn, New York General Dispensary, U. S. Army, New York.
SCHEINBERG, Louis, 1st Lieut., Brooklyn, Fort Hancock, N. J.
SHEARER, Thomas P., 1st Lieut., New York, Fort Dix, N. J.
TRUCKENMILLER, Roy, Major, Freeland, Pa., Camp Lee, Va.
VASSOS, George A., Jr., 1st Lieut., New York, Fort Dix, N. J.
WIRTH, Herman E., 1st Lieut., Brooklyn, Induction Station, Queens, New York.
ZEHNER, David E., 1st Lieut., Brooklyn, Fort McClellan, Ala.

## THIRD CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Third Corps Area, up to January 17. The Third Corps Area comprises the states of Pennsylvania, Virginia, District of Columbia and Maryland.

BLAZINA, William Marion, 1st Lieut., McKeesport, Pa., New Cumberland, Pa.
CLELAND, Charles Edward, Captain, Kane, Pa., Carlisle Barracks, Pa.
COFFMAN, Milton Buell, Lieut. Col., Richmond, Va., Army Medical Center, Washington, D. C.
DEAN, James Seay, Captain, Pennhurst, Pa., New Cumberland, Pa.
DIXON, Charles Warren, Major, Export, Pa., Camp Pendleton, Va.
ECKHARDT, John Carl, Lieut. Col., Washington, D. C., Fitzsimons General Hospital, Denver.
FEINMAN, Jack Irwin, 1st Lieut., Philadelphia, Fort McClellan, Ala.
HIXSON, Clayton Howard, Major, Chevy Chase, Md., Camp Lee, Va.
IMBRIGLIA, Joseph Ettore, 1st Lieut., Philadelphia, Fort McClellan, Ala.
JOHNSTON, Clarence Frederick, 1st Lieut., Baltimore, Denver.
KOHN, David Francis, 1st Lieut., Mount Pocono, Pa., Fort McClellan, Ala.
KOLMER, George August Leonard, Major, Salem, Va., Medical Field Service School, Carlisle Barracks, Pa.
MACKOWIAK, Stephen Casimir, 1st Lieut., Dundalk, Md., Fort McClellan, Ala.
MAINZER, Francis Stanislaus, Major, Huntingdon, Pa., Army Medical Center, Washington, D. C.
MANGES, John Paul, 1st Lieut., Scotland, Pa., Fitzsimons General Hospital, Denver.
McNITT, Henry John Russell, Major, Washington, D. C., Denver.
MONTGOMERY, Robert Sterling, 1st Lieut., South Hill, Va., Fort Belvoir, Va.
MUIR, Bennett W., 1st Lieut., Baltimore, Denver.
PLESSET, Marvin Robert, 1st Lieut., Pittsburgh, Indiantown Gap, Pa.
SAGE, Bernard Anthony, 1st Lieut., Harrisburg, Pa., Denver.
SAYLOR, Lloyd Elwood, 1st Lieut., Baltimore, Fort McClellan, Ala.
SOLOSKO, Alexander, Captain, Salisbury, Pa., Camp Pendleton, Va.
SUGERMAN, Joseph Richard, 1st Lieut., Pittsburgh, Denver.
WALKER, Gale Havard, Captain, Polk, Pa., Fort George G. Meade, Md.

## FOURTH CORPS AREA

The following medical reserve officers had been ordered to active duty up to January 10 by the Commanding General, Fourth Corps Area, comprising Tennessee, North Carolina, South Carolina, Alabama, Georgia, Mississippi, Florida and Louisiana.

DASPIT, Dudley, Jr., 1st Lieut., Houma, La., Fort McClellan, Ala.
DERRICK, Clifton J., 1st Lieut., West Palm Beach, Fla., Fort McClellan, Ala.
DOWELL, Carr T., Jr., 1st Lieut., Baton Rouge, La., Fort McClellan, Ala.
GOLDSMITH, Edward F., Jr., 1st Lieut., Toulminville, Ala., Fort McClellan, Ala.
JERVEY, Allen Jones, Jr., 1st Lieut., Tryon, N. C., Fort McClellan, Ala.
JOHNSON, Roy L., 1st Lieut., Douglas, Ga., Fort McClellan, Ala.
LOGAN, James G., 1st Lieut., Natchez, Miss., Fort McClellan, Ala.
LONG, Thomas W., 1st Lieut., Newton, N. C., Fort McClellan, Ala.
MOSLEY, Robert S., 1st Lieut., Miami, Fla., Fort McClellan, Ala.
O'DELL, John C., Jr., 1st Lieut., Jacksonville, Fla., Camp Blanding, Fla.
O'NEAL, Buford L., 1st Lieut., Shreveport, La., Fort Jackson, S. C.
PAINTER, William W., 1st Lieut., Spartanburg, S. C., Fort McClellan, Ala.

### Orders Revoked

The officers whose names are printed in the adjoining column, and who were previously reported, have been relieved from duty or their orders have been revoked.

CANIPELLI, Edward, 1st Lieut., Jacksonville, Fla.
CHERRY, James H., 1st Lieut., Asheville, N. C.
HOUSER, Frank M., 1st Lieut., Macon, Ga.
NEVANS, Herman B., 1st Lieut., Livingston, Tenn.
SAMS, Frank H., 1st Lieut., Reynolds, Ga.
WACHTEL, Leo M., Jr., 1st Lieut., Jacksonville, Fla.
YOUNG, Henry D., Jr., 1st Lieut., Bushnell, Fla.

## EIGHTH CORPS AREA

The following additional medical reserve officers had been ordered to active duty by the Commanding General, Eighth Corps Area, up to January 11. The Eighth Corps Area comprises the states of Colorado, Arizona, New Mexico, Oklahoma and Texas.

ARMSTRONG, Hiram E., 1st Lieut., Pueblo, Colo., Fort Bliss, Texas.
ARONOFF, Billie L., 1st Lieut., Dallas, Texas, Fort Bliss, Texas.
ARRINGTON, John Hodge, Jr., 1st Lieut., Wichita Falls, Texas, Station Hospital, Fort Sam Houston, Texas.
BICKLEY, Estill T., 1st Lieut., Corpus Christi, Texas, Station Hospital, Fort Sam Houston, Texas.
BUCHTEL, Henry A., 1st Lieut., Denver, Station Hospital, Fort Sam Houston, Texas.
BUSH, Walter H., 1st Lieut., Dallas, Texas, Fort Bliss, Texas.
COCKRELL, John A., Captain, Houston, Texas, Fort Crockett, Texas.
CURTIS, Wickliffe R., Captain, El Paso, Texas, Fort Bliss, Texas.
DOZIER, Fred S., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.
EMENHISER, Lee K., Captain, Oklahoma City, Station Hospital, Fort Sam Houston, Texas.
FARNESS, O. J., 1st Lieut., Tucson, Ariz., Fort Bliss, Texas.
FRENCH, A. James, 1st Lieut., Ann Arbor, Mich., Station Hospital, Fort Sam Houston, Texas.
FRISSELL, Ben P., Captain, Phoenix, Ariz., Fort Bliss, Texas.
HUGHES, Raymond P., 1st Lieut., El Paso, Texas, Station Hospital, Fort Sill, Okla.
IRELAND, Paul M., Captain, Pueblo, Colo., Station Hospital Fort Sam Houston, Texas.
JOHNSTON, Lawrence Walton, 1st Lieut., Terrell, Texas, Station Hospital, Fort Sam Houston, Texas.
JONES, Edmund D., Captain, Beaumont, Texas, Fort Bliss, Texas.
MASON, Porter K., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.
MITCHELL, Holland C., Captain, San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.
PATTERSON, Casey E., 1st Lieut., Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.
PERRY, James H., 1st Lieut., Fredericksburg, Texas, Fort Bliss, Texas.
POWER, Paul H., Captain, Waco, Texas, Fort Bliss, Texas.
SANGER, Welborn W., 1st Lieut., Oklahoma City, Okla., Station Hospital, Fort Sam Houston, Texas.
SCALES, John G., Captain, Dallas, Texas, Fort Bliss, Texas.
SIMMONS, Lillard Nolan, 1st Lieut., Wichita Falls, Texas, Station Hospital, Fort Sam Houston, Texas.
SPILLANE, John H., Jr., 1st Lieut., Colorado Springs, Colo., Fort Clark, Texas.
STECKLER, Milton I., 1st Lieut., Houston, Texas, Fort Bliss, Texas.
STEVENS, Thomas Hood, 1st Lieut., Sulphur Springs, Texas, 45th Division, Fort Sill, Okla.
STOWERS, Aubrey E., 1st Lieut., Sentinel, Okla., 45th Division, Fort Sill, Okla.
STUART, Samuel E., Captain, Dallas, Texas, Fort Bliss, Texas.
STURM, Charles E., Captain, San Antonio, Texas, Station Hospital, Fort Sam Houston, Texas.
TALLEY, John E., Captain, Hamilton, Texas., 45th Division, Fort Sill, Okla.
WALKER, Charles E., Jr., Captain, Denver, Station Hospital, Fort Sam Houston, Texas.
WILKINSON, Robert T., 1st Lieut., Rotan, Texas, Station Hospital, Fort Sam Houston, Texas.
WILLIS, Raymond S., Captain, Dallas, Texas, Station Hospital, Fort Sam Houston, Texas.
WILSON, Charles Hugh, 1st Lieut., Oklahoma City, 45th Division, Fort Sill, Okla.

### Orders Revoked

Orders on the following officers, previously reported, have been revoked:

DOYLE, William H., Captain, Muskogee, Okla.
HARRISON, Ben F., Jr., 1st Lieut., Dallas, Texas.
LEDBETTER, William Harry, 1st Lieut., Wichita Falls, Texas.
LEWIN, Julian R., 1st Lieut., Redvale, Colo.
MONROE, M. L., 1st Lieut., Jasper, Texas.
RICHIE, George T., 1st Lieut., Denver.
SMITH, Haskell, 1st Lieut., Stillwater, Okla.
SWITZER, Fred D., 1st Lieut., Hugo, Okla.
VAN SICKLE, Rayburn Jefferson, 1st Lieut., Longview, Texas.

## NINTH CORPS AREA

The following additional medical reserve officers had been ordered to extended active duty by the Commanding General, Ninth Corps Area, up to January 18. The Ninth Corps Area comprises the states of Washington, Montana, Oregon, Nevada, Utah, California and Idaho.

ACKERMAN, Frederick F., 1st Lieut., Seattle, Fort Lewis, Wash.
ALSBERG, Marden A., 1st Lieut., Glendale, Calif., Nacimiento, Calif.
BASSETT, John W., 1st Lieut., San Diego, Calif., 7th Division, Camp Ord, Calif.
BISCHOFF, George H., 1st Lieut., Boise, Idaho, Buckho Ranch, March Field, Calif.
CANNON, Espey F., 1st Lieut., Salt Lake City, Fort Douglas, Utah.
CLAWSON, Thomas A., Major, Salt Lake City, Fort Douglas, Utah.
DANIELE, Joseph A., 1st Lieut., Hollywood, Calif., Buckho Ranch, March Field, Calif.
DUNCAN, John J., 1st Lieut., West Los Angeles, Calif., Buckho Ranch, March Field, Calif.
FALK, Harry, Captain, Visalia, Calif., Buckho Ranch, March Field, Calif.
JANTZEN, Roland R., 1st Lieut., Redding, Calif., Antiaircraft Firing Center, Riverside, Calif.
JEANS, Virgil E., 1st Lieut., Fresno, Calif., Buckho Ranch, March Field, Calif.
LOWELL, Lawrence M., 1st Lieut., Astoria, Ore., Fort Stevens, Ore.
ROGGE, Edgar A., Captain, Seattle, Fort Lewis, Wash.
WALKER, Ralph J., 1st Lieut., Oakland, Calif., Fort Scott, Calif.
WEINSTEIN, William, 1st Lieut., Everett, Wash., Camp Clatsop, Ore.
WELLS, Howard A., 1st Lieut., Redmond, Ore., Fort Lewis, Wash.
WILMES, Malcolm N., Captain, Woodland, Calif., Office of Corps Area Surgeon, Presidio of San Francisco.
WOOLCOTT, Floyd L., 1st Lieut., Portland, Ore., Fort Worden, Wash.

### Relieved from Duty

CARLILE, Thomas B., 1st Lieut., ordered to Fort Lewis, Wash., Dec. 5, 1940, relieved from active duty January 6.
SHORT, Faulkner A., 1st Lieut., ordered to Fort Worden, Wash., Nov. 14, 194, relieved from active duty January 16.
SORENSON, Edward J., 1st Lieut., ordered to Fort MacArthur, Calif., Dec. 15, 1940, relieved from active duty January 11.

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# NAVAL RESERVE OFFICERS ORDERED TO ACTIVE DUTY

The following additional naval medical reserve officers have been ordered to active duty:

BERNSTEIN, Wilbur B., Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.
BLOEMERS, Harms W., Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.
DANIELS, Willard F., Lieut. (j. g.), M. C.-V. (G.), Huntington, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.
DAVIDOFF, Manuel A., Lieut. (j. g.), M. C.-V. (G.), Paw Paw, W. Va., 8th Med. Company, Fleet Marine Force, Quantico, Va.
DONABEDIAN, George, Lieut. (j. g.), M. C.-V. (G.), New York, 7th Medical Company, Fleet Marine Force, Quantico, Va.
DUNCAN, Charles S., Lieut. (j. g.), M. C.-V. (G.), Huntington, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.
FORSYTHE, Richard M., Lieut. (j. g.), M. C.-V. (G.), Vahalla, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.
FRITCHEN, A. F., Lieut. Comdr., M. C.-V. (S.), Decorah, Iowa, Naval Hospital, San Diego, Calif.
GIESEN, Josef H., Lieut. (j. g.), M. C.-V. (G.), West Haverstraw, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.
HALEY, Peter A., II, Lieut. (j. g.), M. C.-V. (G.), Charleston, W. Va., 8th Medical Company, Fleet Marine Force, Quantico, Va.
HANSON, Harry A., Lieut. (j. g.), M. C.-V. (G.), Rochester, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.
LEES, C. R., Lieut., M. C.-V. (S.), Fort Worth, Texas, Naval Hospital, San Diego, Calif.
MORRISON, A. A., Lieut., M. C.-V. (S.), Portland, Maine, Naval Hospital, San Diego, Calif.
MUNCH, Otto L., Lieut. (j. g.), M. C.-V. (G.), Rochester, N. Y., 8th Medical Company, Fleet Marine Force, Quantico, Va.
PATTERSON, J. K., Lieut., M. C.-V. (G.), Santa Barbara, Calif., Naval Hospital, San Diego, Calif.
VIECELLI, J. D., Lieut. Comdr., M. C.-V. (G.), San Francisco, Naval Hospital, San Diego, Calif.

# ORGANIZATION SECTION

## MEDICAL LEGISLATION

### MEDICAL BILLS IN CONGRESS

*Bills Introduced.*—S. 165, introduced by Senator Sheppard, Texas, proposes to continue in the service of the Army, Navy, Marine Corps and Coast Guard beyond the term of their enlistment those suffering from service connected disease or injury and in need of medical or hospital care until recovery through such medical care and hospitalization. S. 238, introduced by Senator Sheppard, Texas, provides that Reserve officers, Army of the United States, who were called or ordered into active military service by the federal government for extended service in excess of thirty days on or subsequent to Feb. 28, 1925, other than for service with the Civilian Conservation Corps and who are now disabled from disease or injury contracted or received in line of duty while so employed, shall be entitled to receive the same retirement pay and hospital benefits as are now or may hereafter be provided by law or regulation for officers of corresponding grades and length of service of the Regular Army. S. 341, introduced by Senator Walsh, Massachusetts, proposes to authorize the Secretary of the Navy to establish naval hospitals at the naval air stations at Jacksonville, Fla., Corpus Christi, Texas, and San Juan, Puerto Rico; the submarine base, Coco Solo, Canal Zone; the naval station, Guantanamo Bay, Cuba, and the marine barracks, Quantico, Va. S. 397, introduced by Senator Reynolds, North Carolina, proposes to provide domiciliary, medical and hospital treatment to certain former members of the Army, Navy, Marine Corps and Coast Guard. S. 398, introduced by Senator Reynolds, North Carolina, and H. R. 2524, introduced by Representative Van Zandt, Pennsylvania, propose to provide benefits on account of disability or death due to service in the armed forces of the United States in the event of war. H. R. 81, introduced by Delegate Dimond, Alaska, proposes to authorize the Secretary of the Interior to construct in the territory of Alaska or in the continental United States a hospital for the treatment of the insane of Alaska and of such other classes of persons who are insane or who may require mental treatment as the President may designate for care and treatment in the hospital. H. R. 164, introduced by Representative Voorhis, California, proposes to grant permanent and total disability ratings to veterans suffering from severe industrial inadaptability as a result of war service. H. R. 1076, introduced by Representative Shafer, Michigan, proposes to extend the benefits of the United States Employees' Compensation Act to emergency relief employees suffering from occupational diseases. H. R. 1395, introduced by Representative Green, Florida, proposes to construct a marine hospital in Florida. H. R. 1624, introduced by request, by Representative Rankin, Mississippi, proposes to define the terms "permanent and total" or "total permanent" as "any reasonably permanent impairment or defect of mind or body, or both, which prevents the individual from following a substantially gainful occupation, providing that, without prejudice to any other cause of disability or employability, the permanent loss of the use of both feet, of both hands, or of both eyes, or of one foot and one hand, or of one foot and one eye, or of one hand and one eye, or the loss of hearing of both ears, or the organic loss of speech shall be deemed total permanent disability," wherever such terms are used in laws relating to the payment of compensation or pension to veterans of the World War. H. R. 2226, introduced by Representative Bates, Kentucky, proposes to define misconduct, for compensation and pension purposes, as limited to felonious misconduct. H. R. 2230, introduced by Representative Brooks, Louisiana, provides that any veteran of any war, who was not dishonorably discharged and who is suffering from any disability, disease or defect irrespective of whether service connected or not, shall be entitled to receive outpatient treatment at facilities of the Veterans' Administration. H. R. 2245, introduced by Representative Cluett, New York, proposes a federal appropriation of $4,050,000 to construct a veterans' general medical and surgical hospital in one of the counties of Rensselaer, Saratoga, Warren or Washington, in the state of New York, with a capacity of at least one thousand, two hundred beds. H. R. 2283, introduced by Representative McMillan, South Carolina, proposes to extend eligibility for pensions to the widows and children of World War veterans who had disabilities caused or aggravated by examination, hospitalization or medical treatment. H. R. 2299, introduced, by request, by Representative Rankin, Mississippi, proposes to liberalize the benefits for disabled veterans and dependents of deceased veterans. Among other things, the bill provides that any person who served in the military or naval forces of the United States during a recognized campaign or expedition, and who was honorably separated from such service, shall be granted hospitalization, domiciliary care and burial allowances; that retired personnel of the Army, Navy, Marine Corps and Coast Guard, and Fleet Naval and Fleet Marine Corps reservists requiring hospitalization shall be entitled to enter any Army or Navy hospital; that retired enlisted men of the Army, Navy, Marine Corps and Coast Guard when hospitalized or domiciled in either an Army or Navy hospital or United States naval or United States soldiers' home shall be extended such treatment or domiciliary care without cost; and that any veteran of any war who was not dishonorably discharged and who is suffering from any disability, disease or defect, irrespective of whether such disability, disease or defect is service connected, shall be entitled to receive outpatient treatment at facilities of the Veterans' Administration. H. R. 2467, introduced by Representative Izac, California, provides for reciprocal hospitalization in any Army or Navy hospital or domiciliary care in a United States naval or soldiers' home, without cost, to retired or retained personnel of the United States armed forces. H. R. 2475, introduced by Representative May, Kentucky, proposes to prohibit prostitution within such reasonable distance of military or naval establishments as the Secretaries of War or Navy shall determine to be needful to the efficiency, health and welfare of the Army or Navy. H. R. 2601, introduced by Representative Poage, Texas, proposes to create a pension system for adult cripples and for aged citizens. H. R. 2613, introduced by Representative Sheppard, California, proposes a federal appropriation of $500,000 to construct a veterans' hospital in San Bernardino or Riverside County, Calif., to provide facilities to care for the "increasing numbers of disabled veterans of all wars suffering from diseases of the chest." S. 489, introduced by Senator Capper, Kansas, proposes to amend the Social Security Act by adding a new title under which grants will be made to induce states to embark on a combined program of compulsory and voluntary health insurance. This appears to be the hardy perennial sponsored by the American Association for Social Security through Mr. Abraham Epstein. S. 509, introduced by Senator Murray, Montana, proposes to provide for the general welfare by enabling the several states to make more adequate provisions for the control and prevention of industrial conditions hazardous to the health of employees. The bill proposes an appropriation for the fiscal year ending June 30, 1941 of $1,000,000, for the fiscal year ending June 30, 1942 of $2,000,000, for the fiscal year ending June 30, 1943 of $3,000,000, and thereafter an appropriation sufficient to carry out the purposes of the bill. The administration of this bill will devolve on the Secretary of Labor, who must approve all state plans, and a state plan must provide for its administration by the state labor department or other agency charged with the administration of the general labor laws of the state.

## STATE MEDICAL LEGISLATION

### Arkansas

*Bills Introduced.*—H. J. R. 1 proposes so to amend the state constitution as to authorize the construction and operation of a state charity hospital, to consist of one thousand, one hundred beds, in Pulaski County. H. 2 proposes to authorize the establishment and operation of a state cancer institute in Phillips County for the care and treatment of persons suffering from cancer and unable to pay for necessary care and treatment in a private institution or able only to pay such expenses in part. H. 32 proposes to create a state hospital commission of five members to manage and control all institutions maintained by the state for the treatment of mental illness and nervous diseases, including the treatment of persons who are feebleminded, epileptic, drug addicts and suffering from psychoses resulting from alcoholism. The bill proposes that any resident of the state who is mentally ill and in need of hospitalization for such illness shall be eligible for admittance to any appropriate state hospital for diagnosis, care and treatment. The bill proposes that the estate of any patient which is financially able to do so must pay in part for the care rendered that patient.

### California

*Bills Introduced.*—S. 204 proposes that any charitable hospital that has used due care in the selection of its employees shall not be liable for the injury or death of any patient caused by the negligence of such employees, regardless of whether the patient pays in whole or in part for the services he receives. S. 226 and A. 308 propose to make incurable insanity a ground for divorce. H. 245 proposes to require every public or private hospital or school of medicine, surgery or osteopathy to pay any intern in its employ not less than $50 monthly and, in addition, to provide full board and lodging and laundry services and, in the event of illness or injury, to provide medical treatment and hospitalization. A. 208, to amend the workmen's compensation act, proposes that "the term 'physician' or 'practicing physician' shall, at the option of the employer or employee, be construed to include regularly licensed chiropractors and the term 'medical, surgical and hospital services and supplies' shall, at the option of employer or employee, be construed to include services and supplies by regularly licensed chiropractors or chiropractic hospitals." A. 303, to amend the medical practice act, proposes to exempt from the payment of the required annual registration fee a licentiate while (1) engaged in full time active service in the medical corps of the Army, Navy or Marines or in the United States Public Health Service, or (2) "fulfilling his full period of training and active service, whether as a draftee or volunteer, under the Selective Training and Service Act of 1940." A. 380, to supplement the medical practice act, proposes to authorize the revocation or suspension of the certificate of a licentiate who has committed any act constituting or involving lewd conduct, lascivious conduct, immoral conduct or moral turpitude. Assembly Constitutional Amendment 14 proposes a constitutional amendment to enable the legislature to provide for the operation of a statewide lottery, the revenue from which is to be appropriated to the administration and payment of old age benefits and the administration of state hospitals and asylums. A. 413 proposes that the annual directory of licensed physicians which the medical practice act requires the board of medical examiners to compile and distribute shall contain the following additional information: (1) the annual report of the board for the prior year, (2) information relating to other laws of the state and to the United States which the board may determine to be of interest to licentiates and (3) a copy of the California medical practice act.

### Connecticut

*Bill Introduced.*—H. 27 proposes to safeguard the distribution and sale of certain dangerous caustic or corrosive acids, alkalis and other substances by requiring the containers of such articles sold at retail to be labeled with the name of the article, the name and place of the business of the manufacturer, packer, seller or distributor, the word "POISON" in uncondensed gothic capital letters, not less than 24 point size, and directions for treatment in case of accidental personal injury by the substance.

### Indiana

*Bill Introduced.*—S. 24, to amend the workmen's compensation act, proposes, among other things, to require an employer to provide an employee injured in an industrial accident necessary first aid medical and surgical services and all necessary and hospital services thereafter, limited, however, to that which is reasonably required to cure or relieve the effects of industrial injuries. Under the present law the employer is required to furnish such services only during the first ninety days after the occurrence of the industrial accident.

### Iowa

*Bill Introduced.*—S. 2 proposes to condition the issuance of a license to marry on the presentation by each party to the proposed marriage of a physician's certificate stating that, within twenty days prior to the application for a license to marry, the party has been examined and has been found free of syphilis or any stage of that disease whereby it may become communicable. The physician's certificate must be based on a clinical examination and on a standard serologic test for syphilis.

### Kansas

*Bills Introduced.*—H. 1, to amend the osteopathic practice act, proposes (1) to confer on osteopaths the right to practice operative surgery and obstetrics and to administer antiseptics, anesthetics, narcotics and biologics; (2) to provide that after July 1, 1941 applicants for licenses must, in addition to the educational qualifications now required by law, present evidence of the completion of at least one year of preprofessional education of a college grade in a college approved by the board of osteopathic examiners before commencing the study of osteopathy and, after July 1, 1944, present evidence of having completed at least two years of preprofessional education of a college grade; and (3) to permit the board to license without examination applicants who are certificants of the national board of examiners for osteopathic physicians and surgeons. The bill specifically provides that "Each person holding a legal and valid certificate to practice osteopathy in this state at the time of the passage of this act shall without further proof be entitled to receive the certificate to practice as an osteopathic physician and surgeon hereinabove described, and to enjoy the rights and privileges herein provided for a person holding such a certificate." H. 8 proposes to enact a separate naturopathic practice act and to create an independent board of naturopathic examiners to examine and license applicants for such licenses. The bill proposes to describe naturopathy as a "distinct system of healing based upon its own philosophy of health and disease, defined as an art, science, philosophy and practice, following definite physical, chemical, biological, mental and spiritual laws for the restoration and maintenance of health and the correction of bodily disorders without the use of drugs or surgery. For relief and cure it makes use of nature's most beneficent forces and agencies on the theory that under the normal conditions of natural living the body is a self-recuperating organism."

### Massachusetts

*Bills Introduced.*—S. 485, to amend the medical practice act, proposes to add at the end of the section stating the educational qualifications required of applicants for licenses to practice the following: "The board in its examinations of applicants shall have requirements at least as qualifying as the standards of admission recommended by the National Board of Registration in Medicine." S. 498, to amend the old age assistance act, proposes that the old age assistance to be rendered eligible persons "shall include the furnishing of false teeth, eye glasses, hospital and medical services and expenses." H. 804, to amend the workmen's compensation act, proposes to make compensable "heat exhaustion" suffered by a workman in the course of his employment. S. 561, to amend the law regulating the mode in which records must be kept by hospitals supported in whole or in part by contribution from the state or a subdivision thereof and hospitals conducted as public charities, proposes that whenever preexisting hospital records shall have been photographed or microphotographed and the photographs or microphotographs shall have been indexed and filed by the hospital, the person in charge of the hospital, on due notice, may destroy

the original records so photographed or microphotographed, and the photographs or microphotographs shall have the same force and effect as the original records from which they were made. H. 893 proposes that any person, not in an institution, receiving public support, who is in need of the services of a physician may employ any physician who is registered with the department of civil service and that reasonable compensation must be paid such physicians by the town liable for the support of the patient.

### Nebraska

*Bills Introduced.*—Bill 4 proposes that within thirty days after the birth of any child born with visible congenital deformities the physician, midwife or person acting as midwife in attendance of such birth shall prepare and file with the bureau of vital statistics, through the director of health, a statement setting forth such visible congenital deformity. The present law requires a report under such circumstances to be made to the Child Welfare Bureau at Lincoln or to any other state commission, board or division having supervision of crippled children. Bill 35 proposes, in effect, to exempt chiropractic applicants from the provisions of the basic science act. The bill proposes that chiropractic applicants be examined in the basic sciences by the chiropractic board rather than by the basic science board.

### New York

*Bills Introduced.*—S. 154 and A. 140, to amend the workmen's compensation act, propose to permit treatment by public hospitals of workmen's compensation cases when the employer or his insurance carrier refuses or neglects to authorize hospital services and proposes to permit an injured employee to select any hospital for care and treatment in such cases in accordance with rules prescribed by the commissioner. A. 189, to amend the law in relation to the examination of donors of blood for transfusion, proposes to permit the physical examination of such donors within thirty days, instead of ten days, as the law now provides, preceding the offering of such blood donation. A. 243 proposes to require the board of education of each city and of each school district maintaining vocational schools to provide in each vocational high school facilities for health service for the pupils, which health service is to include necessary facilities to afford adequate physical examinations, including roentgenographing of the chest.

### Ohio

*Bill Introduced.*—H. 51 proposes to authorize the formation of corporations not for profit to establish, maintain and operate voluntary nonprofit medical care plans whereby professional services will be provided at the expense of such corporations to such persons or groups of persons as become subscribers to such plan under contracts which will entitle each such subscriber to certain professional services by duly licensed physicians and surgeons in their offices, in hospitals and in the home. The term "professional services" as used in the bill is not to be construed to include hospital services.

### Oklahoma

*Bill Introduced.*—H. 104 proposes to repeal the law prohibiting the retail sale and distribution of certain barbituric acid compounds except on the prescription of a licensed physician, dentist or veterinarian.

### Pennsylvania

*Bills Introduced.*—S. 20 proposes to impose a stated license tax on slot machines or other similar devices of skill or chance. The bill proposes to appropriate the revenue from such taxes to the department of health for crippled children's hospitals. S. 29 proposes to authorize the sexual sterilization of inmates of stated institutions who are feebleminded or are afflicted with incurable chronic mania or dementia. The bill also authorizes the sexual sterilization of any inmate of a penal institution who has been convicted more than once of a sex crime. H. 42 proposes to require the department of revenue on behalf of any hospital in the commonwealth to collect or enforce payment of any account for hospital services rendered to any person because of injuries sustained in a motor vehicle accident. If such payment cannot be enforced by the department and the injured person or his estate is unable to pay for the hospital care necessary, the hospital bill is to be paid by the commonwealth out of the motor license fund.

## OFFICIAL NOTES

### THE CLEVELAND SESSION

#### Fraternity Meetings

Fraternities and alumni groups which have not already made arrangements for their meetings during the annual session of the American Medical Association in Cleveland, June 2-6, should do so at once, as the available facilities are being reserved rapidly. Groups desiring assistance should write to the chairman of the subcommittee on fraternity and alumni reunions, Dr. Hiram O. Studley, 1422 Euclid Avenue, Cleveland, Ohio. The general chairman of the local committee on arrangements for the annual meeting of the Association is Dr. Clyde L. Cummer, 1422 Euclid Avenue, Cleveland, Ohio.

### ADDRESSES BY OFFICIAL STAFF

DR. PAUL C. BARTON:
Feb. 20—South Side B'nai B'rith, Chicago.

DR. W. W. BAUER:
Feb. 1—Women Field Army, the American Society for the Control of Cancer, Indiana Division, Indianapolis.
Feb. 11—Texas Junior College Assembly, Texarkana, Texas.
Feb. 11—Rotary Club, Texarkana, Texas.
Feb. 11—Arkansas Assembly, Texarkana, Ark.
Feb. 11—Public meeting, Texarkana, Texas.
Feb. 12—High school assembly, Athens, Texas.
Feb. 12—Literary Club, Athens, Texas.
Feb. 12—Henderson County Medical Society, Woman's Auxiliary, Athens, Texas.
Feb. 13—Lamar County Medical Society, Woman's Auxiliary, Doctors' Day Program, Paris, Texas.
Feb. 14—Two high school assemblies, Paris, Texas.
Feb. 21—Advisory Committee on Child Welfare, National Congress of Parents and Teachers, New York.
Feb. 25-26—Joint Committee on Health Programs in Education of the National Education Association and the American Medical Association, Symposium, Atlantic City, N. J.

DR. MORRIS FISHBEIN:
Feb. 5—Luncheon, National Social Hygiene Day, Chicago.
Feb. 16—National Conference on Medical Service, Chicago.
Feb. 26—Executives Club, Quincy, Ill.

MR. WILLIAM HOLLOWAY JR.:
Feb. 5—Woman's Auxiliary to Peoria Medical Society, Peoria, Ill.
Feb. 16—National Conference on Medical Service, Chicago.
Feb. 17—Chicago Medical Society Woman's Auxiliary, Stock Yards Branch.
Feb. 18—Congress on Medical Education and Licensure, Chicago.

DR. FRANK H. LAHEY:
Feb. 24—Palm Beach County Medical Society, Palm Beach, Fla.

DR. NATHAN B. VAN ETTEN:
Feb. 9—South Side Clinical Society, Chicago.
Feb. 22—Minisink Historical Society, Port Jervis, N. Y.

### RADIO BROADCASTS

"Doctors at Work" is the title of the sixth annual series of dramatized radio programs being presented by the American Medical Association and the National Broadcasting Company.

The series opened Wednesday, November 13, and will run for thirty consecutive weeks, closing with a broadcast from the

A. M. A. meeting at Cleveland on June 4. The program is scheduled for 10:30 p. m. eastern standard time (9:30 central, 8:30 mountain, 7:30 Pacific time) over the Blue network, other N. B. C. stations and Canadian stations.

The programs are broadcast on what is known in radio as a sustaining basis; that is, the time is furnished gratis by the radio network and local stations, and no revenue is derived from the programs. Therefore local stations may or may not take the programs, at their discretion, except those stations which are owned and operated by the National Broadcasting Company.

Some radio stations may be unable to broadcast the program at the regular scheduled time and may transcribe and broadcast it at another hour or even on another day. It is advisable therefore to verify the time by reference to local newspapers or by telephoning the local Blue network stations.

The programs will dramatize what modern medicine offers the individual in the way of opportunities for better health and the more successful treatment of disease. Incidental to this main theme the programs will explain the characteristics of the different fields of modern medicine and its specialties.

Descriptive posters for local distribution may be had gratis from the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Program titles will be announced weekly in THE JOURNAL and monthly in *Hygeia*, the Health Magazine.

Tickets are available for each broadcast. Address the Bureau of Health Education, American Medical Association, 535 North Dearborn Street, Chicago. Tickets are free, but a stamped self-addressed envelop should accompany requests.

The next three programs to be broadcast, together with their dates and titles, are as follows:

February 5. New Faces For Old.
February 12. Medical Detective.
February 19. One Man's Poison.

The following stations are broadcasting "Doctors at Work" as of January 21:

| | | | |
|---|---|---|---|
| Akron, Ohio | WAKR | Montreal | CFCF |
| Albany, N. Y. | WABY | New York | WJZ |
| Altanta, Ga. | WAGA | Ocala, Fla. | WTMC |
| Baltimore | WBAL | Orlando, Fla. | WLOF |
| Bay City, Mich. | WBCM | Plattsburg, N. Y. | WMFF |
| Beaumont, Texas | KFDM | Providence, R. I. | WEAN |
| Birmingham, Ala. | WSGN | Pueblo, Colo. | KGHF |
| Bridgeport, Conn. | WICC | Salt Lake City | KUTA |
| Chicago | WENR | Seattle | KJR |
| Columbia, Mo. | KFRU | Shenandoah, Iowa | KMA |
| Daytona Beach, Fla. | WMFJ | Sioux City, Iowa | KSCJ |
| Des Moines, Iowa | KSO | Spokane, Wash. | KGA |
| Dubuque, Iowa | WKBB | Springfield, Ill. | WCBS |
| Erie, Pa. | WLEU | Springfield, Ohio | WIZE |
| Flint, Mich. | WFDF | Toledo, Ohio | WTOL |
| Fort Wayne, Ind. | WOWO | Washington, D. C. | WMAL |
| Greenwood, Miss. | WGRM | Youngstown, Ohio | WFMJ |
| Jackson, Mich. | WIBM | Charlestown, W. Va. | WGKV |
| Jackson, Miss. | WSLI | Clarksburg, W. Va. | WBLK |
| Jacksonville, Fla. | WJHP | Dayton, Ohio | WING |
| Jamestown, N. Y. | WJTN | Fort Worth, Texas | KGKO |
| Kansas City, Mo. | WREN | Madison, Wis. | WIBA |
| Lansing, Mich. | WJIM | Reading, Pa. | WRAW |
| Miami Beach, Fla. | WKAT | Sioux Falls, S. D. | KELO |

# WOMAN'S AUXILIARY

## New Jersey

The Woman's Auxiliary to the Atlantic County Medical Society was held, October 18, with Mrs. Anthony G. Merendino presiding. Mr. Frank McBroom spoke on the "Community Chest."

The Woman's Auxiliary to the Hudson County Medical Society opened its season's activities, October 8, at Jersey City. A board meeting was held in the morning and plans for the year's work and social activities were discussed. This was followed by lunch and bridge. Miss Sadie James, executive director of the Jersey City American Red Cross, spoke on the many activities carried on by the chapter and appealed for the cooperation of the members.

Mrs. Louis Viteri presided at the October meeting of the Burlington County auxiliary, at which time past presidents were presented with pins and corsages.

Forty members and guests were present at the October meeting of the Camden County auxiliary, which met at the home of the president, Mrs. L. L. Glover. Guest speaker was Mr. Harry F. Roye, of Haddonfield, a member of the New Jersey state legislature, who talked on "Children of Today in the World of Tomorrow."

The Woman's Auxiliary to the Essex County Medical Society opened the season with a luncheon meeting, October 28, with an attendance of seventy members, three new ones. Mrs. J. Irving Fort, president, presided. Volunteers were called on to work at the Newark City, Newark, Beth Israel, St. Barnabas and Orange (N. J.) Memorial hospitals and the Academy of Medicine, registering visiting physicians at the fall clinical conference, November 27 and 28.

## Tennessee

The Memphis auxiliary met in October with forty-six new members present. An interesting debate on the issues of the presidential campaign was the feature of the program, planned by Mrs. W. T. Pride. Mrs. Thomas Nelson Coppedge and Mrs. Harry Anderson were the speakers.

Dr. Lois Kennedy spoke on "Allergy" at the meeting of the Woman's Auxiliary to the Rutherford County and Stones River Medical Society held recently at "Shadowlawn," the country home of Dr. and Mrs. J. A. Scott. The annual membership tea of the auxiliary to the Nashville Academy of Medicine and the Davidson County Medical Society was held at the home of Mrs. Frank Fessey.

## Washington

The auxiliary to the King County Medical Society held its membership tea in Seattle in October with one hundred and fifty members present. At the September meeting one hundred and seventy-six members were present, and Mrs. R. E. Mosiman, President-Elect of the Woman's Auxiliary to the American Medical Association gave reports of the national meeting in New York.

The auxiliary to the Spokane County Medical Society met in October. Mrs. C. L. Lyon, public relations chairman, gave a report on the national, state and local candidates and how they stood in regard to medicine. Fifteen dollars was voted to the Spokane Community Chest Fund, and plans made to aid several needy families. Units were appointed to help at Red Cross headquarters one day every week. At the September meeting Mrs. G. E. Hoxsey, state president, was the guest speaker.

The auxiliary to the Pierce County Medical Society held a membership tea in October. At the September meeting Mr. A. E. Anderson, executive secretary of the Washington State Medical Association, spoke on legislation in regard to candidates favorable to medicine in both state and county tickets. Mrs. George Nace was appointed chairman of the welfare project to supply reading material and children's clothing to the Lakeview Tuberculosis Sanatorium.

The Walla Walla Valley Medical Society auxiliary met in October. Mrs. G. E. Hoxsey, president of the state auxiliary, spoke. Other speakers were Mrs. H. A. Mount, Dr. Homer Dudley, president of the state medical association, W. T. Laube, attorney for the association, and Arthur Anderson, executive secretary of the association.

The auxiliary to the Yakima County Medical Society met in October. Guest speakers were Mrs. G. E. Hoxsey, president of the state auxiliary, and Mr. Oscar Schuman, who talked on legislative bills of interest to the medical profession. It was reported that a net profit of $134.70 from a rummage sale had been turned over to the children's ward at St. Elizabeth's Hospital.

The Clark County auxiliary met in October at Vancouver. *Hygeia* contest rules were reported. The guest speaker was Dr. I. C. Munger Jr., president of the Clark County Medical Society, who gave a talk on the present day setup of the medical profession in the army.

# Medical News

(PHYSICIANS WILL CONFER A FAVOR BY SENDING FOR THIS DEPARTMENT ITEMS OF NEWS OF MORE OR LESS GENERAL INTEREST: SUCH AS RELATE TO SOCIETY ACTIVITIES, NEW HOSPITALS, EDUCATION AND PUBLIC HEALTH.)

## CALIFORNIA

**Annual Postgraduate Assembly.** — The seventh annual postgraduate assembly of the College of Medical Evangelists, Los Angeles, was held December 8. Among the speakers were:

Dr. Henry Borsook, Pasadena, Vitamins: Their Place in Nutrition and Therapy.

Dr. Walter Scott Franklin, Santa Barbara, External Diseases of the Eye with Differential Diagnosis in Conjunctivitis, Iritis and Glaucoma.

Karl F. Meyer, Ph.D., San Francisco, The General Practitioner and Virus Infections of the Central Nervous System.

Drs. Burrell O. Raulston and Harold J. Magnuson, Los Angeles, Treatment of Early Syphilis by the Continuous Drip Method.

Dr. Harold Lincoln Thompson, Los Angeles, Traumatic Perforation of the Intestine, with Report of Cases.

A symposium on the role of vasodilator, vasospastic and antispasmodic drugs in cardiac, gastrointestinal, genito-urinary and peripheral vascular disturbances was presented by Drs. William Paul Thompson, Alva Claude Surber Jr. and Roy J. Popkin, Los Angeles.

## COLORADO

**National Youth Health Program.** — A statewide health project will be set up under the sponsorship of the Colorado State Board of Health as a part of a health program now being established by the National Youth Administration of Colorado for its out-of-school youth. The primary purpose will be to provide health examinations to NYA out-of-school youth on projects throughout the state, to cooperate with local agencies in arranging for necessary reparatory work and to maintain health records for the individual youths. The program is to be directed by a state medical consultant who will be employed on the administrative staff of NYA and will be compensated at the rate of $18 a day on a one-fourth time basis. The state medical society through its public policy committee is cooperating with the NYA in the organization of the program and in the selection of the state medical consultant and a supervisor, the latter to work under the direction of the consultant.

## ILLINOIS

**Public Health Association.**—The Illinois Public Health Association was organized at Springfield on December 5 at a meeting called for that purpose by local health officers and others interested. The association is a voluntary agency, the object of which is to promote interest in public and individual health, according to the *Illinois Health Messenger*. Officers are Dr. Arlington Ailes, health officer of LaSalle, Peru and Oglesby, president; Barter K. Richardson, senior administrative officer, state department of public health, vice president, and Dr. Howard A. Orvis, health officer of Winnetka, secretary.

**The State Needs Physicians.**—The state department of public health has openings for young physicians who wish to make public health work their career. Five of these physicians are scheduled to begin a year's training at a recognized school of public health in February, all expenses to be paid by the state and federal governments. At the end of their training the physicians will be eligible to take civil service examinations for district health superintendent and other public health service positions. Persons who are accepted for the training course are required to pledge themselves to remain in public health work for three years. The maximum age limit on applicants is 35 years. The state department also has openings for nine young physicians who are to be placed as assistants to the superintendents in district health offices, with the training course being made available to them next year. Applications may be sent to the state director of health, Statehouse, Springfield.

### Chicago

**Dr. Herrick Will Give Fenger Lecture.**—Dr. James B. Herrick will deliver the fifth Christian Fenger Lecture of the Institute of Medicine of Chicago and the Chicago Pathological Society at the Palmer House, February 10. His subject will be "Christian Fenger as I Knew Him, 1885-1902: A Study in Personality."

**The Bacon Lectures.** — Prof. Henrik Dam of the Biochemical Institute, University of Copenhagen, will deliver the Charles Sumner Bacon Lectures for 1940-1941 at the University of Illinois College of Medicine. Professor Dam will speak February 12 at 1 p. m. on "Vitamin K, Its General Significance in Biochemistry," and February 13 at 4 p. m. on "Vitamin K, Its Role in Human Pathology and Its Application in Therapeutics."

**Course in Electrocardiographic Interpretation.** — A course in electrocardiographic interpretation for graduate physicians will be given at Michael Reese Hospital by Dr. Louis N. Katz, director of cardiovascular research. The class will meet each week for twelve weeks, beginning February 19. Additional information and a copy of the program may be obtained by writing to the Cardiovascular Department, Michael Reese Hospital.

**National Social Hygiene Day.** — The Illinois Social Hygiene Association will hold a special program at the Palmer House February 5 to observe National Social Hygiene Day. Dr. Irving S. Cutter, dean, Northwestern University Medical School, will be chairman at the luncheon meeting. The afternoon program will be given over to four phases of social hygiene: medical, educational, law enforcement and social protective measures.

**Psychiatric Meeting.**—The Illinois Psychiatric Society will meet at the Medical and Dental Arts Building February 6. The speakers will be: Drs. Emma Sylvester-Pollaczek on "Clinical Examples of Child Psychotherapy"; Lloyd H. Ziegler and Merle Q. Howard, Wauwatosa, Wis., "Psychoses and Allied States Occurring Subsequent to Thyroidectomy," and Alexander R. MacLean, Rochester, Minn., "Treatment of Orthostatic Hypotension and Orthostatic Tachycardia on the 'Head-Up' Bed."

## KANSAS

**Society News.** — The Northwest Kansas Medical Society was addressed at Colby recently by Drs. Clarence R. Schmidt, Halstead, on "The Role of Hepatic Physiology in the Preoperative Preparation of Patients"; William S. Walsh, Halstead, "The Value of the Hippuric Acid Test of Liver Function in Thyroid Disease," and Charles Douglas Deeds, Denver, "Heart Failure."——Dr. Philip W. Morgan, Emporia, discussed heart disease before the Wabaunsee County Medical Society in Eskridge recently. —— The Wyandotte County Medical Society was addressed, December 17, in Kansas City by Drs. Louie F. Barney on "Modern Concepts of Wounds and Their Treatment" and William H. Algie, "The Clinical-Neurological Examination." Both are of Kansas City. The society was addressed, January 21, by Drs. Edgar F. DeVilbiss and Lee H. Leger, Kansas City, on "Use of Metrazol in Treatment of Mental Diseases" and "Headaches and Head Pain," respectively.——Dr. Henry H. Turner, Oklahoma City, addressed the Sedgwick County Medical Society, Wichita, January 21, on "Present Status of Endocrinology in General Practice."——Dr. Arthur D. Gray addressed the Shawnee County Medical Society in Topeka, January 6, on "Sulfanilamide and Its Derivatives in the Treatment of Genito-Urinary Infections."

## KENTUCKY

**Personal.**—Dr. William J. Gerding, Newport, was honored with a testimonial dinner December 12 by his colleagues on the staff of St. Elizabeth's Hospital, Covington, and representatives of the hospital's school of nursing. The dinner marked Dr. Gerding's completion of twenty-five years as instructor in materia medica in the school of nursing and thirty-two years on the staff of the hospital. Dr. Philip H. Dorger, Covington, was toastmaster.

**Society News.** — Dr. James M. Kinsman, Louisville, addressed the Bourbon County Medical Society, Paris, December 19, on "The Present Status of Sulfanilamide, Sulfapyridine and Sulfathiazole."——Speakers at a meeting of the Muldraugh Medical Society December 12 were Drs. Harry S. Andrews, Louisville, on "Pneumonia in Children"; Ruel T. Routt, Sonora, "Home versus Hospital Treatment of Pneumonia," and Samuel A. Overstreet, Louisville, "Chemotherapy in Pneumonia."

**Changes in State Hospital Administration.**—Dr. Addie M. Lyon, superintendent of the Western State Hospital, Hopkinsville, has been appointed director of state hospitals and mental hygiene to succeed Dr. Joseph G. Wilson, Frankfort, resigned. The appointment was made by W. A. Frost, recently appointed state commissioner of welfare. Dr. William R. Summers, superintendent of the Central State Hospital, Lakeland, will succeed Dr. Lyon at Hopkinsville and Dr. Isham Kimbell,

manager of the Veterans Administration Facility at Gulfport, Miss., will come to the Lakeland hospital. Dr. Lyon was recommended for the state directorship by an advisory committee of the Kentucky State Medical Association.

## MICHIGAN

**The Beaumont Lectures.**—Dr. Armand Quick, associate professor of pharmacology, Marquette University School of Medicine, Milwaukee, will deliver the annual Beaumont lectures of the Wayne County Medical Society, February 3 and 10. His subject will be "The Coagulation of the Blood and Its Relation to Hemorrhagic Diseases."

## MISSOURI

**Society News.**—Dr. Owen S. Gibbs, Memphis, Tenn., will discuss "Drug Poisoning and Its Management" before the Kansas City Academy of Medicine, February 21.——Dr. Carl H. B. Schutz, Kansas City, discussed "Anatomical Routes of Infection To and From the Urinary Tract" before the Kansas City Urological Society, January 9.——Dr. Edward Lee Dorsett, St. Louis, discussed "Why Is It Necessary to Reoperate in Certain Gynecological Cases?" before the Kansas City Society of Obstetrics and Gynecology, January 9.

**Dr. Crossen Honored.**—Dr. Harry Sturgeon Crossen, since 1935 professor emeritus in gynecology at Washington University School of Medicine, St. Louis, was guest of honor at a dinner given at the university on November 23. Dr. George Gray Ward, New York, the guest speaker, discussed "The Advances in Gynecology in the Past Fifty Years." On the same day the St. Louis Obstetrical and Gynecological Society gave a luncheon to Dr. Ward, when he spoke on "Carcinoma of the Cervical Stump Following Hysterectomy."

**Professor Schmidt Goes to Massachusetts.**—Francis O. Schmidt, Ph.D., Rebstock professor of zoology, Washington University, St. Louis, has been appointed professor of biology in charge of the program in biologic engineering at the Massachusetts Institute of Technology, according to the New York *Times*. Dr. Schmidt is expected to advance the close cooperation between the institute's department of biology and public health and the departments of physics, chemistry and electrical engineering. This broad program of education and research in biologic engineering is going forward under a grant of $200,000 from the Rockefeller Foundation. Dr. Schmidt took his doctor's degree at Washington in 1927 and after some work abroad returned to his alma mater in 1929 as assistant professor of zoology.

## MONTANA

**Dr. Cox Receives Theobald Smith Award.**—The 1940 Theobald Smith award in medical science was presented to Herald R. Cox, Sc.D., principal bacteriologist of the U. S. Public Health Service, Hamilton, during the recent meeting of the American Association for the Advancement of Science in Philadelphia. Dr. Cox, who is stationed at the Rocky Mountain Laboratory of the public health service, received the award "for his outstanding research in the rickettsial diseases, resulting in the development of a new technic for the preparation of protective vaccines against Rocky Mountain spotted fever and typhus fever." In 1931 Dr. Cox graduated at Johns Hopkins University, Baltimore, where he served for a time as instructor in immunology. He also served as assistant in bacteriology and pathology at the Rockefeller Institute for Medical Research, New York. He was appointed associate bacteriologist in the public health service in 1936 and promoted to principal bacteriologist in 1940. The Theobald Smith Award was established in 1935 by Eli Lilly and Company, to be bestowed on an investigator under 35 years of age for "demonstrated research in the field of medical sciences, taking into consideration independence of thought and originality." The award consists of a bronze medal and $1,000.

## NEW JERSEY

**Hospital Changes.**—Dr. Herbert McC. Wortman, assistant superintendent of Mountainside Hospital, Montclair, has been appointed superintendent to succeed Dr. Charles H. Young, who has been appointed administrator of Jefferson Hospital, Birmingham, Ala.——Dr. Thomas Howell, superintendent of Overlook Hospital, Summit, has resigned, it is reported.

**Society News.**—Dr. Lewis D. Stevenson, New York, addressed the Hudson County Medical Society, Jersey City, January 7, on "Recent Advances in the Diagnosis and Treatment of Diseases of the Nervous System."——A symposium on diseases of the thyroid gland was presented before the Morris County Medical Society, Morris Plains, January 16, by Drs. Frank H. Pinckney, George H. Lathrope and George J. Young, Morristown.——Drs. Harvey B. Matthews, Brooklyn, and Arthur W. Bingham, East Orange, addressed the Gloucester County Medical Society, Woodbury, January 16, on "Management of Prolonged Labor" and "Lessons to Be Learned from a Study of Maternal Mortality" respectively.

**Prosecutions by State Board.**—The state board of medical examiners recently reported the following cases of illegal practice and the results of prosecutions, among others:

Wellington A. Allen, Plainfield, who posed as a physician, pleaded guilty and was sentenced to ten days in jail.

Michael Nogradi and Philip Manna, unlicensed chiropractors of New Brunswick, paid penalties for practicing without a license.

Andrew V. Pulcrano, Lakewood, paid the penalty for practicing without a license.

Frank Crawford, Williamstown, a registered pharmacist, paid a penalty for practicing medicine without a license.

Florence Goldstein, a herbalist of Passaic, paid the penalty for practicing without a license.

Francis X. Halligan, Toms River, a registered pharmacist, paid the penalty for practicing medicine without a license.

Harold Singer, Jersey City, a licensed chiropodist who exceeded his license by giving electrical treatments and manipulations, paid a penalty for practicing without a license.

**Medical Preparedness in Case of Disaster.**—The medical preparedness division of the mayor's security committee of Elizabeth has outlined a plan for medical action in the event of a disaster. Buildings near each hospital have been selected to be used as reception centers if hospitals overflow their capacities. In case of a greater emergency, seven churches will be used as overflow stations. The medical setup will be under the supervision of a "medical director," who will coordinate work of the physicians with the police, the Red Cross, the hospitals and the transportation committee. The director will appoint teams to man the reception centers while other physicians go direct to the scene of the emergency. Detailed plans have been worked out for emergency treatment and transfer of injured to hospitals and reception centers. Definite arrangements must be made with the Red Cross to provide adequate equipment for the emergency teams, a trained civilian corps of ambulance drivers, stretcher bearers and clerks, nurses and a central joint headquarters for the Red Cross officer and the medical director. Dr. Rocco M. Nittoli, Elizabeth, is chairman of the medical preparedness committee.

## NEW YORK

**Expanded Case Finding Tuberculosis Program.**—A special coordinating committee has been appointed by Dr. Edward S. Godfrey Jr., state health commissioner, to launch an expanded case finding and control program in an effort to eradicate tuberculosis in New York State outside of New York City. The committee includes Drs. Robert E. Plunkett and Vivian A. Van Volkenburgh and Miss Marion Sheahan of the state health department, Albany; Dr. William J. Tiffany, Albany, state commissioner of mental hygiene; Dr. Peter Irving, New York, secretary of the Medical Society of the State of New York; Dr. Donald B. Armstrong, New York, third vice president, Metropolitan Life Insurance Company; David C. Adie, state commissioner of social welfare; Homer Folks, LL.D., secretary; George J. Nelbach, executive secretary, and Robert W. Osborn, assistant executive secretary of the State Charities Aid Association, New York. The committee's efforts will be directed toward examination of contacts, examination of persons with typical symptoms, case finding among susceptible groups and more effective utilization of hospitalization to break the chain of infection, it was reported.

### New York City

**Academy to Increase Endowment.**—The New York Academy of Medicine has begun a five year program to raise funds to carry on its activities, Dr. Malcolm Goodridge announced on the occasion of his inaugural address beginning his second term as president. The academy needs $500,000 for changes in the library and for support of the annual budget. It is hoped to increase the endowment fund by $1,250,000 in the five years under the leadership of a committee with Dr. Harold R. Mixsell as chairman. Dr. Goodridge pointed out that a deficit of $18,000 for the year ended Dec. 31, 1939 had been met by a gift from Mr. Bernard M. Baruch.

**Association of Dermatosyphilologists.**—Formation of the Association of Dermatosyphilologists of Greater New York is announced. Officers are Drs. Howard Fox, president; George Miller MacKee, president-elect, and Maurice J. Costello, secretary. Purposes of the society were announced as follows: appointment of a dermatosyphilologist to the medical

advisory boards in the national defense program; adjustment of difficulties in connection with workmen's compensation; efforts to seek cooperation of hospital officers and physicians in charge of outpatient departments in directing compensable dermatoses to private physicians; elimination of violations of the medical practice act by lay practitioners and corporations in treatment of cutaneous diseases, and clarification of the status of the dermatosyphilologists under the various prepayment medical service plans.

## OHIO

**Ophthalmologist Leaves Funds for Research.**—The residuary estate of the late Dr. Walter H. Snyder, Toledo, which is valued at $350,000, has been released by court action for the establishment of the Snyder Ophthalmic Foundation to provide funds for research in diseases of the eye. By trust agreements made several years ago Dr. Snyder and his wife, who died in 1937, placed the bulk of their property in trust and directed that on their deaths the funds should be used for research in ophthalmology and other charitable purposes. Following Dr. Snyder's death in 1938 the will was contested by relatives. The research funds are to be administered by five directors, including Drs. Conrad Berens and John H. Dunnington, New York.

**Society News.**—Dr. Frank Dennette Adams, Boston, will address the Mahoning County Medical Society, Youngstown, February 18, on "Some Clinical Considerations of Chronic Headache."——Speakers at the meeting of the Summit County Medical Society, Akron, January 7, included Drs. Elgie R. Shaffer, Columbus, "The Vaccine or Serum Treatment of Whooping Cough"; Paul R. Adams, Akron, "The Relationship of Coronary Disease of the Heart to Heart Disease in General," and William McK. Johnston, Akron, "Surgery of the Thyroid."——Dr. Warfield M. Firor, Baltimore, addressed the Academy of Medicine of Cincinnati, January 7, on "Use of Sulfanilylguanidine in Surgery."——Dr. Clarence O. Sappington, Chicago, addressed the Montgomery County Medical Society, Dayton, January 17, on "Modern Appraisal of Industrial Medicine."

## PENNSYLVANIA

**Biologist Dies.**—David Hilt Tennent, Ph.D., research professor of biology at Bryn Mawr College, Bryn Mawr, died January 14, aged 67. Dr. Tennent had been associated with the college since 1904 and had conducted investigations in many parts of the world. He had served as president of the American Society of Zoologists and the American Society of Naturalists.

### Pittsburgh

**Symposium on Public Health.**—The Allegheny County Medical Society presented a symposium on public health and preventive medicine at its meeting, January 21. Dr. John J. Shaw, state secretary of health, made an address of welcome, and the speakers were Drs. Huntington Williams, Baltimore, on "New Aspects of Municipal Health Administration"; John M. Campbell Jr., Harrisburg, "Recent Advances in Control of Communicable Diseases"; Chauncey L. Palmer, Pittsburgh, "The Physician's Interpretation of Public Health Laws in Allegheny County and Pennsylvania," and Charles Howard Marcy, Pittsburgh, "The Problem of Tuberculosis Control in Pittsburgh and Allegheny County."

## RHODE ISLAND

**Society News.**—Drs. John B. Sears, Boston, and Seebert J. Goldowsky addressed the Providence Medical Association, January 6, on "Phlebitis, Ulcers, the Thromboses" and "Modern Treatment of Varicose Veins" respectively.——Dr. Henry S. Joyce, Providence, was recently elected president of the Hospital Association of Rhode Island and Dr. Harmon P. B. Jordan, Providence, vice president.

## WEST VIRGINIA

**Conference of County Society Officers.**—The annual conference of county medical society secretaries and presidents of the West Virginia State Medical Association was held in Charleston, January 18. The speakers were:

Dr. Robert K. Buford, Charleston, president of the state association, Our 1941 Medical Program in West Virginia.
Major Luther R. Lambert, Fairmont, state medical officer for selective service, The Doctor and Preparedness.
Dr. Carl M. Peterson, director, Council on Industrial Health, American Medical Association, Chicago, Industry and Health.
Dr. Ward Wylie, Mullens, Medical Legislation.
Mr. William J. Burns, executive secretary, Michigan State Medical Society, Lansing, Michigan's Voluntary Medical Insurance Plan.
Dr. Russel Kessel, Charleston, Medical Organization and Public Affairs.

## WISCONSIN

**Nursing Services in Industry.**—The state board of health and the industrial nurses of Wisconsin are sponsoring a symposium on industrial public health nursing services, which will be held at the Hotel Wisconsin, Milwaukee, February 20-22. Dr. Paul A. Brehm, Madison, supervisor of the industrial hygiene unit of the state board of health, is general chairman of the program, which includes the following speakers:

Dr. Stanley J. Seeger, Milwaukee, chairman, Council on Industrial Health, American Medical Association, Relationship of the Nurse in Industry to the Physician.
J. J. Bloomfield, U. S. Public Health Service, Washington, D. C., Responsibility of the Nursing Profession in Industrial Hygiene.
Mr. Harry Guilbert, safety director, the Pullman Company, Chicago, The National Defense Program and the Industrial Worker.
Dr. Norbert Enzer, Milwaukee, Relationship of Cardiovascular Diseases to Accidents.
Dr. Richard D. Mudd, Saginaw, Mich., and Mr. W. G. Hazard, Owens-Illinois Glass Company, Toledo, Absenteeism in Industry.

There will be two panel discussions, one on "After the Injury—What?"; the other, "Community Resources as They Concern the Nurse in Industry."

**Society News.**—The Hon. Alexander P. Wiley, U. S. Senator from Wisconsin, addressed the Medical Society of Milwaukee County, December 12, on "Changing Social Conditions and Their Effect on the Future of Medicine"; the incoming president, Dr. Timothy J. Howard, Milwaukee, gave his official address.——Dr. Robert L. Bennett Jr., Madison, addressed the Brown-Kewaunee-Door County Medical Society, Green Bay, December 16, on physical therapy in rheumatoid arthritis.——Drs. Charles F. Burke and Herbert W. Virgin Jr., Madison, addressed the Dane County Medical Society, Madison, December 10, on "Treatment of Congestive Heart Failure" and "Experimental Replacement of Long Bone Shafts with Vitallium" respectively.——Dr. John A. Schindler, Monroe, addressed a joint meeting of the Green and Lafayette county medical societies in Monroe, December 13, on "Treatment of Alcoholic Cirrhosis of the Liver."——Dr. Elmer L. Sevringhaus, Madison, addressed the La Crosse County Medical Society, La Crosse, December 17, on "Menstrual Irregularities and Sterility."——Dr. Robert E. Burns, Madison, discussed "Trauma of the Back" at a meeting of the Rock County Medical Society, Janesville, December 17.——Dr. Milton C. Borman, Milwaukee, addressed the Winnebago County Medical Society, Oshkosh, January 2, on "Practical Handling of Rheumatism."——Dr. Andrew C. Ivy, Chicago, addressed the University of Wisconsin Medical Society, Madison, January 17, on "Bile Acid Metabolism and Therapy."

## GENERAL

**The Influenza Outbreak.**—The U. S. Public Health Service reported January 23 that, up to January 18, 120,006 cases of influenza had been reported in the United States, a rise of 30,178 in one week. It was reported January 11 that 18,000 school children in Boston were ill with a mild form of the disease. Classes had been suspended in Salem, Haverhill and Gardner, Mass., and in Augusta, Me. One lumber camp deep in the Maine woods reported nearly a third of the lumberjacks had influenza and colleges in Maine were said to have suspended social activities and sports events. Outbreaks were also reported in Georgia, Louisiana, Arkansas and Tennessee. In Chicago, the health commissioner reported that 80 cases of influenza had been reported this year up to January 21 as compared with 47 for the previous year. In New York 84 cases were reported January 23 for the preceding twenty-four hours, a decline from 140 reported two days before. The health department considered that the prevalence had not reached the proportions of an epidemic.

**"Medical Pilots."**—The group known as "Medical Pilots" has printed its by-laws, which state that the organization is to be devoted to the mutual enjoyment and advancement of aviation among doctors of medicine. It is not a military organization and, when the present shortage of airplanes is ended, the organization hopes to make group flights. At present it holds monthly dinners to which noted aviation personalities in commercial and military circles are invited. The emblem, "Wings on the Caduceus," shall be worn only by active pilot members or by members who have been active pilots, the by-laws provide. The associate and honorary members wear no insignia. The Charter Hangar may grant the use of the name "Medical Pilots" to other organizations of medical pilots outside the county of Los Angeles by a majority vote of the members, provided the use of the name and insignia are granted only to organizations which adopt the principles of the Charter Hangar as their own. All members of "Medical

Pilots" shall conform to the principles of medical ethics of the American Medical Association and to the rules and regulations of the U. S. Department of Commerce, Bureau of Air Commerce. The secretary is Dr. Colby Hall, 1136 West Sixth Street, Los Angeles, Calif.

**Grants Available from the Plotz Foundation.** — The Ella Sachs Plotz Foundation announces that applications for grants to be held during the year 1941-1942 must be in the hands of the executive committee by April. These grants are usually less than $500. Researches will be favored that are directed toward the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery. The grants may be used for purchase of apparatus and supplies needed for special investigations and for unusual expenses but not for materials that are ordinarily a part of laboratory equipment. There are no formal application blanks, but letters must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money. Applicants should state whether they have approached other foundations for financial assistance. Letters of recommendation from the directors of the departments in which the work is to be done are desirable. The foundation reports that in the past year it made twenty-three grants. Eighty-one applications were received, fifty-one from the United States and the others from fifteen countries. Of the grants one went to China, one to Argentina and the remainder to investigators in the United States. In the seventeen years of its existence the foundation has made three hundred and ninety-four grants.

# *Government Services*

## Positions for Physiotherapy Aides

The U. S. Civil Service Commission announces open competitive examinations for the positions of physical therapy aide, paying $1,800 a year, and for junior physical therapy aide, paying $1,620 a year. Applications must be on file with the commission not later than February 17 and 20, the later date being for applicants living west of Colorado. Information and application forms may be obtained from the secretary of the board of civil service examiners at any first or second class post office or from the commission at Washington, D. C.

## Meeting of Advisory Cancer Council

The National Advisory Cancer Council held a session at the new National Cancer Institute laboratory at Bethesda, Md., January 6. Dr. Ludvig Hektoen, executive director of the council, reported that during the last three years grants-in-aid totaling $271,277.50 have been made. Applications for grants which would have totaled $1,995,635.25 were considered, it was said. Of the amount granted $129,085 was for fundamental cancer research, $49,652.50 for clinical cancer research and $92,570 for experimental work in connection with the cyclotron. Carl Voegtlin, Ph.D., chief of the National Cancer Institute, reported that the institute now has a staff of thirty-eight scientists and fifty technicians trained for specific investigations. Dr. Cornelius P. Rhoads, director of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, and Edward A. Doisy, Ph.D., professor and director of the department of biochemistry, St. Louis University School of Medicine, were recently named as members of the advisory council and Dr. Hektoen was reappointed executive director.

## Public Health Assistants Needed

The U. S. Civil Service Commission announces examinations to fill the positions of psychiatric nurse, guard-attendant and medical technical assistant in the division of mental hygiene of the U. S. Public Health Service. Applicants for the position of psychiatric nurse, which pays $3,200 a year, must be registered graduate nurses with experience in a hospital for mental patients. They will not be required to take a written test. Applicants for the medical guard attendant positions must be registered graduate nurses, with experience as attendant at federal penal or correctional institutions or service in the army or navy medical corps. The salary is $1,620 a year. For medical technical assistant positions, applicants must meet the requirements for the guard attendants and in addition must have had one year of training or experience in either clinical laboratory technic, pharmacy or roentgen ray laboratory technic. Applications must be filed at the Washington office of the civil service commission not later than February 17 and 20, the later date being for applications sent from Colorado and states westward. Information may be obtained from the secretary, U. S. Board of Civil Service Examiners, at any first or second class post office, or from the commission at Washington, D. C.

## Advisory Council on Mental Diseases

The Advisory Council on Nervous and Mental Diseases, appointed by Dr. Thomas Parran, surgeon general, U. S. Public Health Service, Washington, met December 16 in Washington. Establishment of a national institute for research on these diseases, similar to the National Institute of Health and the National Cancer Institute, was proposed. Grants-in-aid to other institutions were also suggested as a means of furthering research. Members of the advisory council are:

Dr. Edward A. Strecker, professor of psychiatry, University of Pennsylvania School of Medicine, Philadelphia.

Dr. Nolan D. C. Lewis, medical director, New York State Psychiatric Institute and Hospital, New York.

Dr. Lloyd H. Ziegler, associate medical director, Milwaukee Sanitarium, Wauwatosa, Wis.

Dr. Abraham Myerson, clinical professor of psychiatry, Harvard Medical School, Boston.

Dr. Arthur H. Ruggles, secretary, American Psychiatric Association, Providence, R. I.

Dr. Henry W. Woltman, consultant on neurology, Mayo Clinic, Rochester, Minn.

Dr. Robert Findlay Gayle Jr., professor of neuropsychiatry, Medical College of Virginia, Richmond.

Dr. Parran, ex officio chairman of the council, presided at the meeting and Drs. Lawrence Kolb, assistant surgeon general in charge of the division of mental hygiene, U. S. Public Health Service, and Winfred Overholser, superintendent of St. Elizabeths Hospital, took part in the discussions.

## Prohibit Solicitation by Lawyers in Government Hospitals

According to an announcement of the Surgeon General of the United States Public Health Service (Federal Register **5**:5220 [Dec. 21] 1940) the regulations for the government of the U. S. Public Health Service have recently been amended. This amendment prohibits the solicitation in hospitals of the U. S. Public Health Service of legal business or of a retainer or agreement authorizing an attorney to perform or render legal services. It is made the duty of the medical officer in charge, on learning of any such solicitation, to make an appropriate investigation and, if satisfied that such has occurred or is occurring, within ten days submit a detailed report to the surgeon general for appropriate action. All persons in the employ of or attached to any hospital of the U. S. Public Health Service and all patients confined therein are forbidden to communicate, directly or indirectly, with any attorney, or any person acting in behalf of such attorney, for the purpose of aiding, assisting or abetting such solicitation. However, a patient is not to be prevented from communicating with an attorney of his choice on his own behalf. No person shall knowingly be permitted to enter such a hospital for the purpose of negotiating a settlement or obtaining a general release or a statement, written or oral, from a patient within fifteen days after confinement, with reference to any personal injuries for which such patient was confined therein, unless prior to the procuring of such release or statement the injured party has signified to the medical officer in charge his willingness that such be given. All persons in the employ of or attached to any hospital of the U. S. Public Health Service and all patients confined therein are also forbidden to communicate, directly or indirectly, with any one attempting to procure such a settlement, release or statement. It is provided, however, that these prohibitions shall not apply to any release or statement obtained by or on behalf of the attorney of the person so confined and shall not prevent the medical officer in charge from giving information essential to the negotiation of a settlement. Any employee of the U. S. Public Health Service who violates any provision of this amendment to the regulations shall be immediately relieved from duty and be subjected to such further disciplinary action as is provided in the regulations. Furthermore, any patient of the U. S. Public Health Service who violates any of these provisions shall be subject to discharge for disciplinary reasons in accordance with the procedure provided by the regulations.

# Foreign Letters

## SWITZERLAND

*(From Our Regular Correspondent)*

Dec. 17, 1940.

### Bombs Which Fell in Geneva

Dr. Jentzer, professor of surgery, before the medical society of Geneva, analyzed the nature of the lesions caused by the bombs that fell in the city last June. About a dozen of the injured were brought to the surgical clinic of the university. In 7 cases there were slight dotlike wounds caused by metal or stones. Several were wounded while they were in bed. One woman's breast was torn away while on a balcony; in another case the subscapular artery was severed. Two deaths occurred. In 1 case there was only a superficial wound in the thorax. At necropsy, however, two ribs were found pulverized and the powder in the lungs. In the other case a lesion occurred in the left gluteal area and the rectum. The entrance wound was small, but there was extensive internal damage and rapid infection.

### The International Committee of the Red Cross

Several representatives of the International Committee of the Red Cross, all Swiss citizens, were active in war-torn sections of Europe, Asia and Africa. Dr. Roland Marti visited various Belgian, British, French and Polish prison camps in Germany. M. R. Haccius flew to England to visit German war prisoners and interned civilians and to pave the way for a greater cooperation of the International Red Cross with Great Britain. Mr. Collart inspected camps of interned German civilians in Syria; Georges Vaucher visited interned Italian civilians in Egypt; Dr. Marcel Junod, in the occupied section of France, sought the cooperation of military authorities for improving the conditions of interned war prisoners, especially by allowing prisoners to correspond with their relatives and by allowing visits of representatives of the International Red Cross. He visited several depots in which French prisoners were temporarily housed and a hospital in the northern part of France in which British and French wounded were cared for. He discussed plans with Prof. Pasteur Vallery Radot, the new president of the French Red Cross, for aid to war prisoners and in Paris met the director of the national information bureau for war prisoners.

### Physiology of Digestion in Nurslings

Dr. E. Freudenberg, professor of pediatrics in Basel, spoke before the medical society of that city on the subject of the physiologic factors in the digestion of nurslings. His observations showed (1) that the mortality rate of children is highest at the nursling age and lowest between the years of 10 and 15 years, (2) that digestive and nutritional disturbances formerly constituted a principal cause of mortality in the early stage and that (3) nursling mortality is significantly affected by the use of cow's milk. Freudenberg found that mother's milk remains only a short time in the infant's stomach and that the digestion is stimulated already by a small amount of gastric juice secretion. Cow's milk, on the other hand, requires a larger quantity of gastric juice. The digestion of the albumin contained in mother's milk proceeds with extraordinary economy in time and acidity. A low acidity in the stomachs of nurslings also accompanies the splitting up of fats when mother's milk is employed, because mother's milk contains a lipase not found in cow's milk. By means of the jejunal probe, Freudenberg was able to study fermentation in the small intestine and confirmed his earlier observations that mother's milk is better for the nursling than cow's milk. There is a more rapid decomposition of mother's milk in the intestine. The lactose of mother's milk produces in the intestinal tract of the infant a flora different from that of cow's milk. The breast-fed infant thus needs to expend digestively and nutritionally less energy to accomplish the same ends as the child nourished on cow's milk. This economy in nutritional energy enables breast-fed children to endure intestinal disturbances better. The greater demand made on the digestive apparatus of artificially fed infants entails greater disturbances of the digestion and hence a higher mortality. Numerous detailed investigations have failed to create a standardized form of artificial nutrition.

### A Swiss Ambulance Unit in the Finnish War

Dr. Robert Nicole, assistant physician in the surgical division of the university clinic in Basel and director of the Swiss ambulance unit, made a report to the medical society of Basel on the experiences of the medical expedition. The ambulance unit had been sent on its mission of mercy at the request of the Finnish Republic with the approval of the Federal Council of the Swiss Republic. It consisted of ten physicians, nine nurses and two attendants. It had to be completed on short notice and was ready in a week. The physicians were all native German Swiss. Only surgeons were selected who had been specially trained for war surgery. The difficulties of transportation were enhanced by the fact that a circuitous route had to be adopted by way of Rotterdam to Bergen, Norway, then from Stockholm via Haparanda to Helsingfors, a route of 3,200 kilometers. The equipment, consisting of instruments, medicaments and bandage material, was planned for two months and 500 patients. The ambulance unit carried a complete hospital equipment including x-ray apparatus, sterilization trucks patterned after the Swiss army sterilizers and so on. The complete cost of equipping this medical service amounted to more than 200,000 Swiss francs ($46,430). After the medical mission arrived in Finland, its field of operation was determined in consultation with the head of the Finnish sanitary division and the director of the Finnish Red Cross. Military events made it impossible to carry out the original plan of maintaining the ambulance unit as an independent Swiss unit. Its forces had to be divided. Some were able to give some assistance at the front, others were assigned to different hospitals and military medical stations. Most of the wounded suffered from war lesions five days old. Because of political developments, medical aid at the front could not be practiced for more than a few days.

The kinds of lesions encountered were, generally, similar in their incidence to those of the World War. Maxillary wounds did not show an increase. Among 6,000 wounded there were fifty-six maxillary lesions. Grave head and body wounds were relatively infrequent. Infection was found to set in on the third day, even in small lesions. However, its virulence was not as intense as was observed in traumas due to traffic accidents in Basel. Therapeutic procedure depended not so much on the size of the wound as on its origin. In lesions due to shell and bomb fragments excision was recommended, in lesions due to small arms conservative treatment was advised. Primary suture of war lesions was found to be a mistake because of the infection which regularly occurred. Immobilization was most effective; the use of an ointment of cod liver oil was also helpful. Amputation needs to be done far less than was done formerly. Septic hemorrhages in erosion processes were frequent and were extremely dangerous. Empyema in the joints was common. Wounded who were operated on in the first twenty-four hours often died of shock rather than of their wound. However, mortality from this cause was greatly diminished by means of intravenous narcosis. Few cases of tetanus occurred, as the troops had been prophylactically inoculated. Gas gangrene was

observed only twice. Splinters need not necessarily be removed. In many cases removal was advised against because of subsequent infection.

### Endemic Goiter

Dr. J. Eugster of Zurich, who has long studied the geographic significance of goiter, discussed the subject before the medical society of Basel. Goiter is endemic in the canton of Aargau. Confirmations are based on twenty-five years of observation. Strangely, goiter affects diversely not only certain portions of the same canton but likewise the same villages and even the same houses. Persons living in certain houses were all affected with goiter, while all those who had lived during the course of years in other houses were all free from goiters. Systematic investigation disclosed even more refined differences. In the examination of one thousand and twenty-four persons of one village it was found that 72 and 79 per cent respectively of those who lived on the first floor had goiter, whereas only 58 per cent of those living on the second floor were so affected. In the case of one thousand four hundred persons who had migrated from a district free from goiter, it was found that the next generation showed goiter in proportion to the goiter incidence of the district into which they moved, whether minimal, average or pronounced. In a family which had moved away in 1893 from a district free from goiter to one with an endemic record, it was found that all children born in that region had acquired goiter whereas one child who had not been born there remained free from the disorder. When the same family moved back to its former village, the children of the second generation born there were free from the disease, though their parents had goiter. It is inferred that the fetal period determines the presence or absence of goiter. In large families, subsequently born children showed goiter more plainly. Likewise in persons born in certain years (e. g. 1903 and 1906) the goiter incidence was higher than in other years. Eugster thinks that climatic factors are involved, since trees were observed in both of these years to have developed more vigorous annual rings. Eugster also examined five hundred and eleven pairs of twins. He found that of a pair of twin sisters moving from a region with endemic goiter into one free from it, the one living on the first floor developed goiter, the other living on the second floor did not. In other cases involving twins, one sister moved into an endemic district and contracted goiter; the other moving into one free from goiter remained unaffected. Uniovularity or biovularity did not make a difference. Eugster believes that a number of individual factors are involved. For example, persons living in houses built on a rock foundation remained free from goiter, whereas those living in houses built on rock material originally derived from the same rock basis have for decades been affected with goiter. Goiter is not hereditary. Spontaneous cures, in which no medication is employed, occur frequently.

### Swiss Aid for France

The Swiss Society for War Harassed Children, working in cooperation with American Quakers, has displayed great activity in France. Recently a canteen was opened in the town of Constantine to serve milk to the children of refugees. Four tons of powdered milk was served to children of eight hundred Belgian war refugees sheltered in barracks at Toulouse. Several other milk distribution centers have been established, and additional tons of condensed and dried milk have been supplied. Children bring their own bread.

### Personals

Dr. F. R. Nager, professor of otorhinolaryngology in Zurich and dean of the medical faculty, delivered the Semon Lecture at the University of London. This is the first time that a Swiss was invited.

Dr. Louis Michaud, professor of internal medicine at the University of Lausanne, celebrated his sixtieth birthday. The *Schweizerische medizinische Wochenschrift* honored the occasion by a festive edition embracing three increased current issues. The *Revue médicale de la Suisse romande* likewise published an issue in his honor. Michaud has been connected with the University of Lausanne as professor and director of the medical clinic since 1913 and has specialized in diseases of the kidneys.

Prof. C. Dorno, climatologist, celebrated his seventy-fifth birthday. In 1907 he created the physicometeorologic observatory at Davos for the investigation of the therapeutic effects of high mountain altitudes. His investigations made him the founder of radiation climatology and medical climatology. The institute founded by him is now maintained at public expense.

Dr. A. Gigon, professor of internal medicine and editor of the *Schweizerische medizinische Wochenschrift,* was elected dean of the faculty of medicine of Basel.

### Deaths

Dr. Max Cloëtta, for many years professor of pharmacology and director of the pharmacologic institute of the University of Zurich, died June 23, 1940, at the age of 72 years. He was a native of Zurich, where he began his academic career in 1898 and advanced rapidly to a professoriate in 1901. Though invited to Göttingen and Munich, he remained in Zurich until 1935, when he retired for reasons of health. With Cloëtta Switzerland's leading pharmacologist passed away, a scholar of international reputation and a man of noble personality.

Dr. Max Askanazy, professor emeritus of pathologic anatomy in the faculty of Geneva, died Oct. 23, 1940, at the age of 75 years. Askanazy was born in East Prussia and began his academic career at the university of Königsberg, joined the faculty of medicine of Geneva in 1905 and served there until his retirement in 1939. His special fields of research were diseases of the blood, malignant tumors and the pathology of bones. He was an excellent teacher. He founded the international society for geographic pathology. In 1935 he was made an honorary citizen of Geneva.

Dr. Eugen Enderlen, for a number of years professor of surgery in Basel, died at the age of 78 in Stuttgart. In 1905 he was called to Würzburg and in 1918 accepted a full professorship to Heidelberg. He specialized in abdominal surgery and blood transfusion.

## Marriages

LOUIS FLEXNER CLEARY, Lexington, Ky., to Miss Cora Leach Kielkopf near Lynchburg, Va., Oct. 3, 1940.

CLAUDE M. MEARS, Lewistown, Mont., to Miss Virginia Maye Cartier at Spokane, Wash., Oct. 8, 1940.

DAVID CROCKER, Fitchburg, Mass., to Miss Mary Bliss Reed of New Haven, Conn., Sept. 14, 1940.

DONALD W. MCCORMICK, Madison, Wis., to Miss Margaret Ann King of Shawano, Sept. 7, 1940.

WILLIAM WIANT DAVIS, Parkersburg, W. Va., to Miss Mary Lydenberg in Baltimore, Oct. 5, 1940.

ARTHUR CALDWELL DUNLAP to Miss Emily Jeannette Mandle, both of Paris, Tenn., Oct. 5, 1940.

ALBERT S. EPPERSON, Cameron, Texas, to Mrs. Jessie Burton Watson of Houston, Oct. 10, 1940.

WILLIAM K. ANDERSON, Saginaw, Mich., to Miss Ethel A. Scott of Bad Axe, Oct. 12, 1940.

RICHARD F. SLAUGHTER, Augusta, Ga., to Miss Jane Carruthers of Winder, Oct. 10, 1940.

JOHN MALCOLM ASTE to Mrs. Jane Boyce Crump, both of Memphis, Tenn., Oct. 3, 1940.

ALLAN L. COHN, Minden, La., to Miss Ruby Mae Foster at Farmerville, Oct. 8, 1940.

CARL W. KUMPE, Covington, Ky., to Miss Ruth Lang of Cincinnati, Sept. 14, 1940.

WILLIAM A. MCMAHON to Miss Barbara Brygger, both of Seattle, Oct. 5, 1940.

# Deaths

**Calvin Richards Hannah** ✠ Dallas, Texas; Illinois Medical College, Chicago, 1904; vice president of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons and member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; past president of the State Medical Association of Texas and the Texas Association of Obstetricians and Gynecologists; professor of obstetrics and head of the department, Baylor University College of Medicine; on the staffs of the Baylor and Parkland hospitals; aged 68; died, Dec. 16, 1940, of coronary thrombosis.

**Harry Quigg Fletcher** ✠ Chattanooga, Tenn.; Johns Hopkins University School of Medicine, Baltimore, 1909; member of the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; past president of the Chattanooga and Hamilton County Medical Society; served during the World War; visiting surgeon on the staff of the Baroness Erlanger and Children's hospitals; aged 57; died, Dec. 7, 1940, of pulmonary embolism following coronary occlusion.

**Mifflin B. Brady** ✠ Cincinnati; Medical College of Ohio, Cincinnati, 1890; associate professor of contagious diseases, University of Cincinnati College of Medicine; member and past president of the city board of health; formerly president of the Certified Medical Milk Commission of the Academy of Medicine; medical examiner of the Probate Court; on the staff of the Cincinnati General Hospital; aged 72; died, Dec. 8, 1940, in the Bethesda Hospital of heart disease and arteriosclerosis.

**Christian Deetjen,** Baltimore; Julius-Maximilians-Universität Medizinische Fakultät, Würzburg, Bavaria, Germany, 1890; member of the Medical and Chirurgical Faculty of Maryland; was a student of Roentgen before the discovery of the roentgen ray and was first to introduce roentgen ray methods in Baltimore; as a result of roentgen ray work lost most of his fingers and later one arm; aged 77; died, Dec. 28, 1940, of arteriosclerosis.

**Nicholas Albert Baltzell** ✠ Marianna, Fla.; Medical Department of Tulane University of Louisiana, New Orleans, 1902; president of the state board of health; past president of the state board of medical examiners; past president of the Florida Railway Surgeons' Association; medical director and owner of a hospital bearing his name; aged 63; died, Dec. 8, 1940, in Jacksonville.

**Ethan Allen Campbell** ✠ Chester, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1905; fellow of the American College of Surgeons; served during the World War; on the staffs of the Taylor Hospital, Ridley Park, Chester Hospital and the J. Lewis Crozer Home and Hospital; aged 62; died, Dec. 4, 1940.

**John Meredith Burgin** ✠ Bedford, Ind.; University of Louisville (Ky.) School of Medicine, 1936; member of the Kentucky State Medical Association; was commissioned a first lieutenant in the medical corps of the United States Army in 1938; retired in 1940 for disability; aged 33; died, Nov. 17, 1940.

**Charles F. Shollenberger,** Denver; Jefferson Medical College of Philadelphia, 1885; member of the Colorado State Medical Society; at one time professor of pediatrics at the Denver and Gross Medical College; formerly on the staff of St. Anthony's Hospital; aged 82; died, Nov. 11, 1940.

**John Gerrit Huizinga** ✠ Holland, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1890; member of the American Academy of Ophthalmology and Otolaryngology; aged 72; died, Dec. 20, 1940, in the Lakeshore Hospital, Lake City, Fla. of a ruptured appendix.

**Joseph A. Capozzi,** New York; Columbia University College of Physicians and Surgeons, New York, 1928; member of the Medical Society of the State of New York; on the staffs of the Harlem and Columbus hospitals; aged 44; died, Dec. 6, 1940, of rheumatic heart disease.

**Frederick Joseph Cox,** Gilbertsville, N. Y.; Albany Medical College, 1892; fellow of the American College of Physicians; aged 74; died, Dec. 5, 1940, in the Flower and Fifth Avenue Hospitals, New York, of bronchopneumonia, gangrene of the left leg and arteriosclerosis.

**Thomas Mayes Hopkins,** Denver; Denver College of Medicine, 1901; member of the Colorado State Medical Society; served during the World War; aged 69; died, Nov. 19, 1940, at the Presbyterian Hospital of splenic thrombosis, myocarditis and hypostatic pneumonia.

**John Crittenden Gorsuch,** Denver; University of the City of New York Medical Department, 1892; member of the Colorado State Medical Society; served during the World War; aged 77; died, Nov. 26, 1940, in the Fitzsimons General Hospital of arteriosclerosis.

**Walter L. Rose,** Woodward, Okla.; Central Medical College of St. Joseph, Mo., 1903; Ensworth Medical College, St. Joseph, 1909; member of the Oklahoma State Medical Association; aged 64; died, Nov. 13, 1940, at Halstead, Kan., of bronchiogenic carcinoma.

**David Laughlin Cowden,** Cambridge, Ohio; Ohio Medical University, Columbus, 1893; member of the Ohio State Medical Association; formerly secretary of the Guernsey County Medical Society; county health officer; aged 73; died, Dec. 6, 1940, of cerebral hemorrhage.

**Joseph Nicholson** ✠ Los Angeles; University of Minnesota College of Medicine and Surgery, Minneapolis, 1903; at one time health officer of Brainerd, Minn.; on the staff of the California Lutheran Hospital; aged 62; died, Nov. 5, 1940, of cerebral thrombosis.

**Samuel Thomas King,** Baldwin, N. Y.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1883; for many years member of the board of health of New York; aged 83; died, Nov. 23, 1940, of myocarditis and arteriosclerosis.

**Robert Emmett Conway,** Indianapolis; Indiana University School of Medicine, Indianapolis, 1916; member of the Indiana State Medical Association; on the staffs of the City Hospital and St. Vincent's Hospital; aged 51; died, Nov. 30, 1940, of coronary occlusion.

**Albion Older Bernstein,** New York; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1939; intern at the Beth Israel Hospital; aged 28; was drowned, Nov. 23, 1940, when his car plunged into the East River.

**Milton Ellsworth Hartman,** Allentown, Pa.; Jefferson Medical College of Philadelphia, 1902; member of the Medical Society of the State of Pennsylvania; on the staff of the Allentown Hospital; aged 63; died, Nov. 28, 1940, of coronary disease.

**Edward Joseph Dailey** ✠ Somerville, Mass.; Tufts College Medical School, Boston, 1904; served during the World War; aged 61; died, Dec. 10, 1940, in the Massachusetts General Hospital, Baker Memorial, Boston, of injuries received in a fall.

**Edmond John Melville,** St. Petersburg, Fla.; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1892; member of the Florida Medical Association; served during the World War; aged 72; died, Nov. 28, 1940, of heart disease.

**Harold Wilson,** Conneaut, Ohio; Dartmouth Medical School, Hanover, N. H., 1896; member of the Ohio State Medical Association; served during the World War; for many years member of the city council; aged 66; died, Nov. 5, 1940.

**Thomas F. Conn,** Monticello, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1906; member of the Mississippi State Medical Association; county health officer; aged 60; died, Nov. 19, 1940, in a hospital at Jackson.

**Adolf Julius Drtina** ✠ Seattle; University of Pittsburgh School of Medicine, 1911; at one time physician in charge of the United States Government Hospital for Natives, Dillingham, Alaska; aged 51; died, Nov. 6, 1940, of coronary thrombosis.

**James F. Noble,** Custar, Ohio; Eclectic Medical Institute, Cincinnati, 1891; aged 70; died, Dec. 2, 1940, in the East Side Hospital, Toledo, of injuries received when the automobile in which he was driving was struck by a train.

**Albert Sylvanus Maxson,** Milton Junction, Wis.; Chicago Medical College, 1882; formerly bank president; trustee of Milton College from 1902 to 1931; aged 83; died, Nov. 7, 1940, of arteriosclerosis and coronary thrombosis.

**George Dewey Sagrera** ✠ Arnaudville, La.; Tulane University of Louisiana School of Medicine, New Orleans, 1929; aged 40; died, Nov. 19, 1940, in a sanatorium at Lafayette of injuries received in an automobile accident.

**James Franklin Cooper,** Edinburg, Ill.; Barnes Medical College, St. Louis, 1901; served during the World War; aged 75; died, Dec. 4, 1940, in the Decatur and Macon County Hospital, Decatur, of cerebral hemorrhage.

**Edgar Montealegre,** New York; Hahnemann Medical College and Hospital of Philadelphia, 1906; Jefferson Medical College of Philadelphia, 1908; aged 57; died, Nov. 1, 1940, of angina pectoris and coronary thrombosis.

**Caroline Herring Dennis,** St. Petersburg, Fla.; Woman's Medical College of the New York Infirmary for Women and Children, New York, 1890; aged 77; died, Nov. 25, 1940, in New York of carcinoma of the rectum.

**John Wilson Boggess Sr.,** Woodville, Ala.; Vanderbilt University School of Medicine, Nashville, Tenn., 1892; member of the Medical Association of the State of Alabama; aged 69; died, Dec. 2, 1940, of heart disease.

**George Suttle Gilder,** Carbon Hill, Ala.; Medical College of Alabama, Mobile, 1893; member of the Medical Association of the State of Alabama; aged 70; died in December 1940 of injuries received in an automobile accident.

**John Yeilding,** Hanceville, Ala.; Chattanooga (Tenn.) Medical College, 1894; veteran of the Spanish-American War; aged 78; died, Nov. 12, 1940, of acute dilatation of the heart, chronic myocarditis and nephritis.

**Swithin Chandler** ✠ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1892; aged 70; died, Dec. 10, 1940, at his home in Strafford, Pa., of arteriosclerosis and chronic myocarditis.

**Mark Watson Emery,** Portland, Ore.; University of Oregon Medical School, Portland, 1915; aged 48; died, Nov. 27, 1940, in the Good Samaritan Hospital of rheumatic heart disease and cerebral embolism.

**François Xavier Albert Chevrier,** Ottawa, Ont., Canada; School of Medicine and Surgery of Montreal, Faculty of Medicine of the University of Laval at Montreal, 1898; aged 65; died, Oct. 16, 1940.

**Frances May Gage Hulbert,** Chicago; Hahnemann Medical College of the Pacific, San Francisco, 1895; aged 75; died, Dec. 17, 1940, of injuries received when struck by an automobile when crossing the street.

**William Stevenson MacLaren,** Princeton, N. J.; College of Physicians and Surgeons, medical department of Columbia College, New York, 1889; aged 74; died, Nov. 29, 1940, of myocardial insufficiency.

**Paul Merino Hunsicker,** Beaver Meadows, Pa.; Medico-Chirurgical College of Philadelphia, 1901; served during the World War; aged 70; died, Nov. 21, 1940, in the Hazleton (Pa.) State Hospital.

**Hugh Francis Bradley,** Jarrettsville, Md.; University of Maryland School of Medicine, Baltimore, 1897; aged 71; died in December 1940 of coronary thrombosis, arteriosclerosis and chronic cholecystitis.

**William E. Menefee,** Cleburne, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1888; member of the State Medical Association of Texas; aged 83; died, Nov. 13, 1940.

**Moses Eason Sherer,** Portland, Ore.; Chattanooga (Tenn.) Medical College, 1908; served during the World War; on the staff of the Veterans Administration Facility; aged 57; died, Nov. 29, 1940.

**John Evans Hanna Jr.,** Knoxville, Tenn.; University of Georgia Medical Department, Augusta, 1890; also a pharmacist; aged 76; died, Nov. 26, 1940, in St. Mary's Hospital of chronic cardiorenal disease.

**Charles Sumner Goodwin,** Syracuse, N. Y.; New York University Medical College, New York, 1896; served during the World War; aged 66; died, Dec. 9, 1940, of lobar pneumonia.

**Victor John Ganey,** Winchester, Tenn.; Wayne University College of Medicine, Detroit, 1940; county health officer; aged 26; died, Nov. 20, 1940, in the Harper Hospital, Detroit.

**Walter James Wellington,** Rye, N. Y.; Long Island College Hospital, Brooklyn, 1896; aged 65; died, Nov. 29, 1940, in the United Hospital, Port Chester, of cerebral embolism.

**Charles Fredric Montgomery,** Los Angeles; Chicago Homeopathic Medical College, 1895; aged 72; died, Nov. 17, 1940, in the Los Angeles General Hospital of pneumothorax.

**Margaret Knickerbocker Preston** ✠ Syracuse, N. Y.; Syracuse University College of Medicine, 1927; aged 49; died, Nov. 24, 1940, of nephritis and rheumatic heart disease.

**Israel Trachtenberg** ✠ New York; College of Physicians and Surgeons, Baltimore, 1915; on the staff of the Bronx Hospital; aged 59; died, Nov. 19, 1940, of brain tumor.

**Haim Solomon Bobroff,** Chicago; University of Moscow Faculty of Medicine, Russia, 1916; aged 49; died, Dec. 16, 1940, of cyanide poisoning, self administered.

**John Ernst Nast,** San Francisco; University of California Medical Department, San Francisco, 1895; aged 78; died, Nov. 12, 1940, of myocarditis and arteriosclerosis.

**Montgomery Merritt Hannum** ✠ Eustis, Fla.; University of Tennessee Medical Department, Nashville, 1910; aged 55; died, Dec. 9, 1940, of coronary thrombosis.

**Ernest W. Ewell,** Rochester, N. Y.; University of Buffalo School of Medicine, 1891; veteran of the Spanish-American War; aged 70; died, Nov. 30, 1940.

**William Fisher Boddie,** Forsyth, Ga.; Meharry Medical College, Nashville, Tenn., 1906; aged 56; died, Dec. 4, 1940, in Macon of cardiovascular renal disease.

**Taylor H. Nichols,** Amory, Miss.; Howard University College of Medicine, Washington, D. C., 1904; aged 61; died, Nov. 27, 1940, of cardiac asthma.

**Alexander MacLeod Brown** ✠ Franklin, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1898; aged 72; died, Nov. 26, 1940.

**Caroline Allen Jones,** San Bernardino, Calif.; Medical Department of Valparaiso University, Chicago, 1905; aged 88; died, Oct. 23, 1940, of senility.

**Edgeworth Stephens Casey,** Birmingham, Ala.; Birmingham Medical College, 1900; aged 63; died, Nov. 12, 1940, of duodenal ulcer and nephritis.

**Charles Augustus O'Connor,** Los Altos, Calif.; Cooper Medical College, San Francisco, 1900; aged 64; died in November 1940 of cerebral hemorrhage.

**Zachary Joseph Clark** ✠ Cherokee, Okla.; Kansas City (Mo.) Medical College, 1900; aged 72; died, Nov. 14, 1940, of carcinoma of the colon.

**George William Roos** ✠ Wellsville, N. Y.; University of Buffalo School of Medicine, 1887; aged 73; died, Nov. 5, 1940, of coronary thrombosis.

**Arthur Jay Sprague,** Los Angeles; Northwestern Ohio Medical College, Toledo, 1888; aged 88; died, Nov. 28, 1940, of cerebral hemorrhage.

**William Arthur Smythe,** Stroudsburg, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1911; aged 52; died, Nov. 22, 1940.

**John A. Mercer,** Chilton, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1887; aged 79; died, Nov. 17, 1940.

**James Fred Rigg,** Niagara-on-the-Lake, Ont., Canada; University of Toronto Faculty of Medicine, 1911; aged 52; died, Nov. 14, 1940.

**Edward Daniel Burtt** ✠ Lincoln, N. H.; Baltimore Medical College, 1900; aged 69; died, Dec. 3, 1940, of cerebral hemorrhage and heart disease.

**Alexander Ardell Jackson,** Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1904; aged 64; died, Nov. 16, 1940.

**Charles H. Ashton,** Franklin, Pa.; Baltimore Medical College, 1905; aged 61; died in November 1940 of cerebral thrombosis.

**Arthur Gladstone Wallis,** St. Catharines, Ont., Canada; Unversity of Toronto Faculty of Medicine, 1905; died, Nov. 18, 1940.

**Herman C. W. Gresens** ✠ Chicago; Rush Medical College, Chicago, 1897; aged 71; died, Nov. 28, 1940, of heart disease.

**Albert G. Austell,** Center, Okla.; Memphis (Tenn.) Hospital Medical College, 1906; aged 80; died, Oct. 28, 1940, of heart disease.

**Pryse Campbell Park,** Durham, Ont., Canada; McGill University Faculty of Medicine, Montreal, 1888; died, Nov. 1, 1940.

**C. M. H. Farrar,** Hillsboro, Tenn.; Nashville Medical College, 1878; aged 92; died, Nov. 11, 1940, of acute nephritis.

**Donald Albert Cameron,** London, Ont., Canada; Trinity Medical College; Toronto, 1895; aged 69; died, Oct. 19, 1940.

**Richard Arthur Byrd,** Edmond, Okla.; Hospital College of Medicine, Louisville, Ky., 1907; aged 58; died, Nov. 18, 1940.

**William H. Martin,** Winter Haven, Fla.; Fort Wayne (Ind.) College of Medicine, 1887; aged 78; died, Nov. 19, 1940.

**W. A. Walden,** Davisboro, Ga.; Atlanta Medical College, 1893; aged 70; died, Nov. 20, 1940, of bronchopneumonia.

**William Kerr,** Toronto, Ont., Canada; Trinity Medical College, Toronto, 1889; aged 81; died, Nov. 18, 1940.

**Clyde Ware Swank,** Chicago; Rush Medical College, Chicago, 1890; aged 76; died, Dec. 6, 1940, of carcinoma.

**J. L. Shirley,** Chattanooga, Tenn.; Chattanooga Medical College, 1896; aged 82; died, Nov. 9, 1940.

**Lewis F. Hamrick,** Baltimore; Baltimore Medical College, 1901; aged 64; died in November 1940.

# Bureau of Investigation

## ANOTHER IMPOSTOR REPEATS

### Aaron Raffelson Found Using Name of New York Physician

In 1934 the Bureau of Investigation published in THE JOURNAL an article dealing with one Aaron W. Raffelson, impostor. Within the past year some one, identified by several as this same Raffelson, has been trying similar activities with a little different approach. This time, instead of using one of his aliases (Aaron Raphael, Donald Clinton Raphael, Aaron Wolf, C. S. Julian, Donald B. Parkinson, Sam Clarkson Parkinson, H. C. Mathers and Aaron Raphaelson) he "borrowed" the name of a New York physician. In previous instances—in New York in 1930 and in Santa Fe, N. M., in 1934—he claimed medical education at New York University, University and Bellevue Hospital Medical College, the University of Oregon Medical School and the State University of Iowa College of Medicine.

The more recent incident occurred at Denver and, needless to say, the impostor claimed as his education that of a prominent New York physician whom he was impersonating. In both instances there was a claim for specialization in psychiatry. The other essential facts, which were dealt with in a previous article in THE JOURNAL, indicate that in 1934 Raffelson was about 23 but looked older, was 5 feet 5½ inches tall, weighed 130 pounds,

Photographs of Raffelson (taken in 1930) published in THE JOURNAL for Dec. 1, 1934, which a Denver physician states are unmistakably those of the individual referred to in this article.

was slim and wiry in build, sometimes wore his hair bright red and other times black, had dark brown eyes, a swarthy complexion, occasionally wore a mustache and invariably went bareheaded. Also mentioned was a fingerprint classification in connection with his arrest for forgery in New York City in 1930. This read $\frac{9\ U}{21\ Ra\ 14}$

In 1934, just as New York officials were about to close in on him again, he left for Santa Fe, N. M. There he spoke on psychiatry before local civic clubs and assisted in the investigation of a murder committed in Santa Fe, testifying under oath that he was a practicing physician and that he had assisted in conducting an autopsy on the deceased. Shortly thereafter he left Santa Fe in an automobile which he had obtained by depositing a worthless check. In view of the fact that the car was later found in El Paso, Texas, it was assumed that he had crossed the Mexican border.

During the past year in Colorado, an individual who has been identified as this same person called at the office of the state board of medical examiners with regard to obtaining a license to practice medicine on the basis of his New York license. When he was told that he must meet the requirements of the Colorado Basic Science Board before he would be eligible to file an application, he did not make any attempt to submit credentials. At about this time he opened an office in Denver and distributed professional cards containing the name of the New York physician and the following legend under the name: "Practice limited to Psychometrics—Child Guidance—By appointment only." As soon as the state authorities obtained this information, he was asked to close his office, which he did. In the meantime, however, he had applied to and had received permission to be admitted to the lecturing staff at the University of Colorado School of Medicine. Subsequently he was again found seeing patients professionally and was informed by the superintendent of a local hospital that he must make application to the staff before he could visit such patients. He filled out a form, using the data of the New York physician whom he was impersonating. In that connection, it developed that the real doctor was still located in New York and actively on duty there. When the impostor was asked to appear before the medical advisory board at the hospital, he attempted to reclaim his application and promptly disappeared from sight, supposedly once again in the direction of the Mexican border.

The files of the Bureau of Investigation contain the names of individuals who have frequently repeated their activities as impostors. With each new offense, publicity is given to them in the hope that the publication of their pictures and the data concerning them will militate against their repeating their performances elsewhere. Most of them, however, are able to get away with repeated offenses of this nature because they permit sufficient time to pass so that few physicians recall the incident.

One important factor which aids these frauds in imposing on the profession and the public is the reasonable assumption on the part of the members of the profession that medicine is such an intricate and detailed science that one who did not possess a knowledge of medicine could not pretend to that knowledge without being discovered almost immediately. Apparently in the present instance a superficial knowledge of science enabled this impostor to pass himself off for a time in Colorado not only as a physician but as a specialist in psychiatry.

## MISBRANDED "PATENT MEDICINES"

### Abstracts of Notices of Judgment Issued by the Food and Drug Administration of the United States Department of Agriculture

[EDITORIAL NOTE.—The abstracts that follow are given in the briefest possible form: (1) the name of the product; (2) the name of the manufacturer, shipper or consigner; (3) the composition; (4) the type of nostrum; (5) the reason for the charge of misbranding and (6) the date of issuance of the Notice of Judgment—which is considerably later than the date of the seizure of the product and somewhat later than the conclusion of the case by the Food and Drug Administration.]

**Acetodyne Tablets.**—Glens Falls Pharmacal Co., Inc., (New York State). Composition: declared on label to contain 2 grains of acetophenetidin per tablet, whereas it possessed none of this drug but did contain 1.91 grains of acetanilid, from which acetophenetidin is derived, but which was not declared on the label; hence misbranded because of false labeling. —[*N. J. 30979; August 1940.*]

**Anti-Rheumatic Fever Compound.**—Modern Drugs, Inc., Philippi, W. Va. Composition: essentially plant drugs, including an alkaloid-bearing drug, small amounts of sodium salicylate, potassium acetate, potassium iodide, alcohol, sugar and water. For rheumatic fever, various forms of rheumatic and muscular pains. Fraudulent therapeutic claims.—[*N. J. 30978; August 1940.*]

**Camfo-Phenol Lotion.**—Modern Drugs, Inc., Philippi, W. Va. Composition: essentially camphor, phenol (31.7 per cent by weight in one sample and 35.5 per cent by weight in the other) with alcohol and iodine. Fraudulently represented as a treatment for infection, wounds, abscesses, boils, burns and ulcers of syphilis, tuberculosis and other debilitating diseases.—[*N. J. 30978; August 1940.*]

**Enrich Organic Iron Hematinic.**—Tam Products, Inc., New York. Composition: essentially small amounts of an extract of an animal product, compounds of sodium and ammonium, chlorides, sulfates and phosphates, a trace of an iron compound, glycerin and water. Biologic tests showed it to contain not more than 2 international units of vitamin $B_1$ per cubic centimeter and not more than 240 Chase-Sherman units of vitamin $B_1$ per fluid ounce. Name falsely represented the article to contain a substantial amount of organic iron; fraudulently represented to enrich blood with iron and to benefit nerves, blood, digestion, vitamin $B_1$ deficiency and some other things.—[*N. J. 30997; August 1940.*]

**Ethacaine.**—Seydel Chemical Co., Jersey City, N. J. Composition: essentially benzoic acid and benzocaine in a petrolatum base, with oxyquinoline present. Not antiseptic when used as directed and hence misbranded as such; further misbranded because fraudulently represented as an effective treatment of ulcers and other skin disorders, for the relief of pain in ulcers and a cure for these and superficial carcinomas, also for relief of itching in eczema and for the quick healing of lesions.—[*N. J. 30981; August 1940.*]

# Medical Examinations and Licensure

## COMING EXAMINATIONS

### NATIONAL BOARD OF MEDICAL EXAMINERS
### EXAMINING BOARDS IN SPECIALTIES

Examinations of the National Board of Medical Examiners and Examining Boards in Specialties were published in THE JOURNAL, January 25, page 330.

### BOARDS OF MEDICAL EXAMINERS

ALABAMA: Montgomery, June 17-19. Sec., Dr. J. N. Baker, 519 Dexter Ave., Montgomery.

ARKANSAS: * *Medical.* Little Rock, June 5-6. Sec., Dr. D. L. Owens, Harrison. *Eclectic.* Little Rock, June 5-6. Sec., Dr. Clarence H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Oral examination* (required when reciprocity application is based on a state certificate or license issued ten or more years before filing application in California). San Francisco, April 16. *Written.* Los Angeles, Feb. 24-27. Sec., Dr. Charles B. Pinkham, 1020 N St., Sacramento.

CONNECTICUT:* *Medical. Written.* Hartford, March 11-12. *Endorsement.* Hartford, March 25. Sec., Dr. Thomas P. Murdock, 147 W. Main St., Meriden. *Homeopathic.* Derby, March 11-12. Sec., Dr. Joseph H. Evans, 1488 Chapel St., New Haven.

DELAWARE: July 8-10. Sec., Medical Council of Delaware, Dr. Joseph S. McDaniel, 229 S. State St., Dover.

DISTRICT OF COLUMBIA: * Washington, May 12-13. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA:* Jacksonville, June 23-24. Sec., Dr. William M. Rowlett, Box 786, Tampa.

GEORGIA: Atlanta, June. Sec., State Examining Boards, Mr. R. C. Coleman, 111 State Capitol, Atlanta.

IDAHO: Boise, April 1. Dir., Bureau of Occupational License, Mr. H. B. Whittlesey, 335 State Capitol Bldg., Boise.

INDIANA: Indianapolis, June 17-19. Sec., Board of Medical Registration and Examination, Dr. J. W. Bowers, Citizens Trust Bldg., Fort Wayne.

KANSAS: Kansas City, June 17-18. Sec., Board of Medical Registration and Examination, Dr. J. F. Hassig, 905 N. 7th St., Kansas City.

KENTUCKY: Louisville, June 5-7. Sec., State Board of Health, Dr. A. T. McCormack, 620 S. Third St., Louisville.

MAINE: Portland, March 11-12. Sec., Board of Registration of Medicine, Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Medical.* Baltimore, June 17-20. Sec., Dr. John T. O'Mara, 1215 Cathedral St., Baltimore. *Homeopathic.* Baltimore, June 17-18. Sec., Dr. John A. Evans, 612 W. 40th St., Baltimore.

MASSACHUSETTS: Boston, March 11-13. Sec., Board of Registration in Medicine, Dr. Stephen Rushmore, 413-F State House, Boston.

MICHIGAN: * Ann Arbor and Detroit, June 11-13. Sec., Board of Registration in Medicine, Dr. J. Earl McIntyre, 202-4 Hollister Bldg., Lansing.

MISSISSIPPI: Jackson, June. Asst. Sec., State Board of Health, Dr. R. N. Whitfield, Jackson.

MONTANA: *Reciprocity.* Helena, March 31. *Written.* Helena, April 1. Sec., Dr. S. A. Cooney, 216 Power Block, Helena.

NEVADA: *Reciprocity with oral examination,* Feb. 3. Sec., Dr. Fred M. Anderson, 215 N. Carson St., Carson City.

NEW HAMPSHIRE: Concord, March 13-14. Sec., Board of Registration in Medicine, Dr. T. P. Burroughs, State House, Concord.

NEW JERSEY: Trenton, June 17-18. Sec., Dr. Earl S. Hallinger, 28 W. State St., Trenton.

NEW MEXICO: Santa Fe, April 14-15. Sec., Dr. Le Grand Ward, 135 Sena Plaza, Santa Fe.

VERMONT: Burlington, Feb. 11. Sec., Dr. W. Scott Nay, Underhill.

WEST VIRGINIA: Charleston, March 3. Sec., Public Health Council, Dr. Arthur E. McClue, State Capitol, Charleston.

WYOMING: Cheyenne, Feb. 3-4. Sec., Dr. M. C. Keith, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: Tucson, March 18. Sec., Mr. Franklin E. Roach, Science Hall, University of Arizona, Tucson.

COLORADO: March 6-7. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

CONNECTICUT: Feb. 8. Address State Board of Healing Arts, 1945 Yale Station, New Haven.

DISTRICT OF COLUMBIA: Washington, April 21-22. Sec., Commission on Licensure, Dr. George C. Ruhland, 203 District Bldg., Washington.

FLORIDA: De Land, June 7. *Applications must be on file not later than May 24.* Sec., Prof. J. F. Conn, John B. Stetson University, De Land.

MICHIGAN: Ann Arbor, Detroit and East Lansing, Feb. 14-15. Sec., Miss Flora E. Dube, East Lansing.

OREGON: Portland, Feb. 15. Sec., State Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

RHODE ISLAND: Providence, Feb. 19. Sec., Division of Examiners, Rev. Nicholas H. Serror, Providence College, Providence.

SOUTH DAKOTA: June. Sec., Dr. G. M. Evans, Yankton.

WISCONSIN: Madison, April 5. Sec., Prof. Robert N. Bauer, 3414 W. Wisconsin Avenue, Milwaukee.

## Arizona October Report

Dr. J. H. Patterson, secretary, Arizona State Board of Medical Examiners, reports the written examination for medical licensure held at Phoenix, October 1-2, 1940. The examination covered 10 subjects and included 100 questions. An average of 75 per cent was required to pass. Six candidates were examined, all of whom passed. Four physicians were licensed to practice medicine by reciprocity. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| University of California Medical School | | (1939) | 85.2 |
| Rush Medical College | | (1938) | 78.1 |
| University of Illinois College of Medicine | | (1940) | 83.2 |
| Johns Hopkins University School of Medicine | | (1939) | 88.3 |
| St. Louis University School of Medicine | | (1938) | 76.5 |
| Columbia Univ. College of Physicians and Surgeons | | (1938) | 81.8 |

| School | LICENSED BY RECIPROCITY | Year Grad. | Reciprocity with |
|---|---|---|---|
| Rush Medical College | | (1930) | Illinois |
| State University of Iowa College of Medicine | | (1934) | Iowa |
| Tulane University of Louisiana School of Medicine | | (1936) | Louisiana |
| University of Wisconsin Medical School | | (1934) | Wisconsin |

## Connecticut July Report

Dr. Thomas P. Murdock, secretary, Connecticut Medical Examining Board, reports the written examination for medical licensure held at Hartford, July 9-10, 1940. The examination covered 9 subjects and included 70 questions. An average of 75 per cent was required to pass. Thirty-six candidates were examined, 17 of whom passed and 19 failed. The following schools were represented:

| School | PASSED | Year Grad. | Per Cent |
|---|---|---|---|
| Yale University School of Medicine | | (1940) | 75.1,* 82.2* |
| George Washington University School of Medicine | | (1938) | 75 |
| Georgetown University School of Medicine | | (1939) | 75.1* |
| Loyola University School of Medicine | | (1940) | 75 |
| Louisiana State University School of Medicine | | (1940) | 78.4 |
| Harvard Medical School | | (1938) | 76.4 |
| Tufts College Medical School | | (1939) | 80.4 |
| Cornell University Medical College | | (1940) | 80.7 |
| New York University College of Medicine | | (1940) | 75.1 |
| Syracuse University College of Medicine | | (1940) | 77.1 |
| University of Cincinnati College of Medicine | | (1939) | 75.3 |
| Temple University School of Medicine | | (1940) | 77 |
| Medizinische Fakultät der Universität Wein | | (1937) | 75.7 |
| Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin | | (1936) | 77 |
| Universität Leipzig Medizinische Fakultät | | (1923) | 75.8 |
| Universität Bern Medizinische Fakultät | | (1936) | 76.1 |

| School | FAILED | Year Grad. | Number Failed |
|---|---|---|---|
| Marquette University School of Medicine | | (1940) | 1 |
| University of Western Ontario Medical School | | (1938) | 1 |
| Laval University Faculty of Medicine | | (1931) | 1 |
| Medizinische Fakultät der Universität Wein | | (1934), (1936), (1937), (1938) | 4 |
| Eberhard-Karls-Universität Medizinische Fakultät, Tübingen | | (1920) | 1 |
| Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin | | (1924) | 1 |
| Ludwig-Maximilians-Universität Medizinische Fakultät, München | | (1925) | 1 |
| Universität Heidelberg Medizinische Fakultät | | (1920) | 1 |
| Universität Leipzig Medizinische Fakultät | | (1932) | 1 |
| Magyar Királyi Erzsébet Tudományegyetem Orvostudományi, Pecs | | (1932) | 1 |
| Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest | | (1938) | 1 |
| Regia Università degli Studi di Bologna. Facoltà di Medicina e Chirurgia | | (1937) | 1 |
| Regia Università degli Studi di Roma. Facoltà di Medicina e Chirurgia | | (1937) | 1 |
| Universität Bern Medizinische Fakultät | | (1937) | 1 |
| Osteopaths † | | | 2 |

Twenty-seven physicians were successful in the oral examination held for endorsement applicants at Hartford, July 23. The following schools were represented:

| School | PASSED | Year Grad. | Endorsement of |
|---|---|---|---|
| Yale University School of Medicine | | (1934), (1938, 2), (1939, 4) | N. B. M. Ex. |
| George Washington University School of Medicine | | (1908) | Iowa |
| The School of Medicine of the Division of the Biological Sciences | | (1937)* | New York |
| Tulane University of Louisiana School of Medicine | | (1937) | Louisiana |
| Johns Hopkins University School of Medicine | | (1936), (1937) | Maryland |
| Boston University School of Medicine | | (1936) | N. B. M. Ex. |
| Harvard Medical School | | (1936), (1937) | N. B. M. Ex. |
| University of Michigan Medical School | | (1937) | Michigan |
| Albany Medical College | | (1939) | N. B. M. Ex. |
| Columbia University College of Physicians and Surgeons | | (1935) | N. B. M. Ex., (1937) New York |
| Long Island College Hospital | | (1927)* | New York |
| University of Rochester School of Medicine and Dentistry | | (1936) | New York |
| University of Tennessee College of Medicine | | (1931) | Tennessee |
| Baylor University College of Medicine | | (1936) | Texas |
| University of Vermont College of Medicine | | (1935)* | N.B.M.Ex., (1937)* Vermont |
| University of Manitoba Faculty of Medicine | | (1935) | Maryland |
| University of Glasgow Medical Faculty | | (1934)* | New York |

* License has not been issued.
† One examined in medicine, the other in medicine and surgery.

# Miscellany

## ACTIVITIES OF NATIONAL FOUNDATION FOR INFANTILE PARALYSIS

The first annual medical meeting of the National Foundation for Infantile Paralysis was held in New York early in November 1940.[1] This meeting was attended by members of the medical advisory committees, the grantees of the foundation, and the board of trustees. Reports on several studies on poliomyelitis virus were made by various investigations supported by the foundation. Virus infected material obtained from the spinal cords of monkeys has been concentrated so that the infection can be produced in dilution of one part to ten million. Studies of the purified and concentrated virus led one investigator to conclude that the virus is protein in nature or contains protein material. Poliomyelitis virus has been found in stools of patients, in contacts and in sewage collected from epidemic areas. Healthy carriers have been found in institutional outbreaks. Attempts to produce infection with poliomyelitis virus in animals other than the monkey have led to confirming previous observations to the effect that the Lansing strain could be made to produce infection in various cotton rats. All but one investigator reported that only this one strain could be made to produce the disease in the cotton rat. He however succeeded in growing several other old as well as newly isolated strains in this species of rat. It was also demonstrated that the virus could be routinely recovered from the central nervous tissue of fatal human cases and from experimental animals and that excepting for tonsils, adenoids and lymph gland tissue no other part of the body was shown to harbor the infection.

So far all attempts at producing immunity, both active and passive, have met with failure. Likewise no chemical agent has been found which will do for poliomyelitis what sulfanilamide and its derivatives have done for certain bacterial infections.

Some studies were reported indicating that the muscular fibrillation resulting from nerve destruction is not the primary cause of atrophy of paralyzed muscle. This point, however, is still controversial. One group of workers reported that occasionally muscles developed a bandlike form of degeneration and that when mattress sutures were used to connect the muscle above and below these bands good functional results could be obtained. Several guides for more accurately testing muscle strength were devised and discussed.

It was concluded from one set of observations that, if the maximum benefits of physical therapy are to be secured for patients after having poliomyelitis, they must be under such care within six months of the onset. They further showed that 97 per cent of all weakened or paralyzed muscles regained the maximum possible strength within eighteen months after onset of treatment. These observations were confirmed by another investigator, who concluded additionally that rest with physical therapy in the hospital has no advantage over family treatments given in the home and that hospital care over long periods is of decided advantage only when underwater treatments are used. Observations on monkeys emphasize the value of rest treatment, since they showed that these animals when forced to exercise during the active disease process had not only a greater amount of paralysis but also a higher death rate.

In addition to these activities largely sponsored by the foundation, studies of epidemics have been made in a few areas and certain assistance has been supplied to communities and hospitals by making splints, Bradford frames and respirators available. Educational activities have been conducted and include an exhibit at the New York World's Fair viewed by more than five million persons and scholarships made available through the National Reserch Council. At the November meeting additional grants were recommended for continuation of existing studies or for new investigations in the amount of $137,350.

1. Report of the First Annual Medical Meeting of the National Foundation for Infantile Paralysis.

# Bureau of Legal Medicine and Legislation

## MEDICOLEGAL ABSTRACTS

**Malpractice: Fragment of Extracted Tooth Lodged in Lung; Res Ipsa Loquitur.**—The plaintiff went to the defendant, an exodontist, on July 3, 1936 for the purpose of having six teeth extracted. At the time of the extractions the plaintiff and the defendant were alone in the defendant's office. The plaintiff was seated in the dental chair and a general anesthetic was administered. When he recovered consciousness the six teeth had been extracted. After he came out from under the anesthetic he noted a heaviness in the right side of the chest which became progressively worse. It was more of an ache than a pain, and the plaintiff felt as though he were taking cold. That evening he commenced to cough and the cough and pain increased in intensity. Two days later he returned to the defendant's office for an examination and the defendant then informed him that he had had "a hard set of teeth to pull" and that they had been broken up quite badly. The coughing and pain continued unabated until April 6, 1937, during which time the plaintiff had suffered many severe hemorrhages from his lungs, the first hemorrhage occurring in December 1936, and he lost about 60 pounds (27.2 Kg.). While eating breakfast on the morning of April 6, he choked and strangled and, after a violent spasm of coughing, he expectorated into a receptacle a quantity of blood and mucus from his lungs which material on examination by his wife was found to contain the root of a tooth. In a subsequent action for damages brought against the defendant dentist, the plaintiff alleged that the fragment of tooth had become lodged in his lung because of the defendant's negligent and unskilful conduct while the plaintiff was unconscious and wholly under the care and management of the defendant. From a directed verdict for the defendant, the plaintiff appealed to the Supreme Court of Iowa.

The defendant contended that the directed verdict was proper because the plaintiff had failed to prove any causal relationship between the alleged negligence of the defendant and the injuries of the plaintiff. The evidence showed that prior to the time the plaintiff coughed up the piece of tooth he had received treatment by many physicians and in many hospitals and had had a number of roentgenograms taken of his lungs and chest. Two of these roentgenograms, taken at St. Luke's Hospital on March 25, 1937 by a Dr. Prouty, revealed a small shadow of increased density in the base or lower posterior portion of his right lung in the region of a "posterior branch of the descending bronchus" on the right side. Dr. Prouty testified that this area of increased density might be a foreign body, or an area of calcification or fibrosis, or "superimposition of thickened bronchi." Other physicians testified in behalf of the plaintiff that his condition was the result of the lodgment of the piece of tooth in his lung. There was also substantial evidence that the plaintiff's condition developed immediately after the extractions and grew progressively worse, and that prior to July 1936 the plaintiff had been a good worker and physically sound. If, said the Supreme Court, the evidence as to the proximate cause of the plaintiff's condition is of sufficient weight, then this question should be submitted to a jury. Such evidence would not be sufficient if it showed merely that the negligence charged might fairly and reasonably have caused the injury if the circumstances shown indicated an equal probability that the injury was due to some other cause. The plaintiff, however, was not required affirmatively to disprove every possible cause of his condition which might be suggested by the defendant.

The court was of the opinion that a jury would be warranted in finding from the evidence which was adduced that the presence of the root of the tooth in the plaintiff's right lung was the proximate cause of his injury. The court believed that the

evidence supported a theory of negligence on the part of the defendant.

If the issue of the defendant's negligence were submitted to a jury, continued the court, the answer would depend largely on whether or not the doctrine of res ipsa loquitur applied. The defendant contended that the doctrine does not apply in a malpractice case against a physician or a dentist because negligence must be shown by the testimony of expert witnesses qualified to state what should or should not have been done. The court admitted that this was a general rule of evidence but said that when the results of an operation are such as are not to be anticipated if reasonable care had been exercised by the operator, then proof of other facts and circumstances having any fair tendency to sustain the charge of negligence will be sufficient to take the question to the jury. The court relied for its decision on *Pendergraft* v. *Royster*, 203 N. C. 384, 166 S. E. 285, in which the following was quoted with approval from Herzog's Medical Judisprudence:

> In many other cases it has been held that mere proof of a mistake or poor results does not itself prove malpractice, but where the injury is received while the patient is unconscious, the doctrine [of res ipsa loquitur] commonly is held to apply because under such circumstances the patient would not be able to testify as to what had happened, whereas the physician could.

In the present case, said the court, we have all the instrumentalities, including the unconscious body of the plaintiff, under the complete and exclusive control of the defendant dentist. We have an occurrence which, according to general knowledge and the defendant's own admission, does not happen in the ordinary course of extraction of teeth if reasonable care is used. We have also a record which might reasonably warrant a jury in finding that it did happen. There is no explanation by the defendant either that it could not have happened or that if it did happen it was through no fault of his, or that it was the fault of the plaintiff himself. The plaintiff, because of his unconscious condition, has no knowledge of what the defendant did or failed to do. Under these circumstances, concluded the court, the doctrine of res ipsa loquitur is applicable and a jury would be warranted in inferring therefrom that the root of the tooth passed into the plaintiff's right lung, through the failure of the defendant to exercise proper care or skill, and caused the plaintiff's injury. The court held, therefore, that the case should be submitted to the jury, and so it reversed the judgment of the lower court.—*Whetstine v. Moravec, 291 N. W. 425 (Iowa, 1940).*

**Compensation of Physicians: Right of Chief of Staff of Hospital to Collect a Personal Fee.**—The defendant, a trolley repairman, was injured in the course of his employment and was taken for treatment to a hospital at which the plaintiff physician was chief of staff or chief surgeon. The defendant's injuries consisted of bruises and contusions and fractures of the second, third, fourth and fifth lumbar vertebrae, but no surgical services were either necessitated or performed. During the defendant's stay in the hospital, Nov. 17, 1930 to Jan. 22, 1931, the plaintiff physician several times visited the ward in which the defendant had been placed but he never talked to him nor personally attended him. According to the defendant, he had no idea that the plaintiff was in any way connected with his case. The evidence showed that all services rendered to the defendant while he was in the hospital were performed by either nurses or interns and that the defendant had been placed in a ward provided for "people who cannot afford to pay." When the defendant left the hospital his entire bill, including charges for bed, board, roentgenograms, medicine and special examination, was paid by his employer. Several months later the plaintiff presented a bill for $100 to the defendant's employer covering, supposedly, the plaintiff's charges for services rendered by him to the defendant during the first thirty days of the defendant's stay in the hospital. On the employer's refusal to pay, the plaintiff physician filed a claim before a workmen's compensation referee, but payment was again refused. He then, about two years after the defendant's discharge from the hospital, forwarded the bill for $100 to the defendant, who likewise refused to pay it. Finally the plaintiff brought suit against the employee to recover the amount. The jury returned a verdict for the defendant, but the trial court set the verdict aside and entered a judgment for the plaintiff. The defendant thereupon appealed to the Superior Court of Pennsylvania.

The plaintiff practically conceded that there was no express promise by the defendant to pay him for the services rendered by him but contended that the defendant was liable because of an implied promise. The plaintiff argued that this implied liability arose (1) because of the fact that the defendant was in the hospital and should have known that the medical services therein were not donated but had to be paid for by some one and (2) because he was chief of staff of the hospital. In answering the first argument the superior court stated that, while there is ordinarily an implied agreement to pay for the services of a physician, if the services were intended to be and were accepted as a gift or act of benevolence they could not at the election of the physician create a legal obligation to pay. The court pointed out that the defendant had been treated while unconscious and had been placed in a general ward. He was never treated by the plaintiff and was not sent a bill until almost two years after he left the hospital. The court held that such circumstances could not raise an implication that the defendant promised to pay the amount claimed. The court further held that the plaintiff's position as chief of staff of the hospital gave him no individual interest in the services of the interns or other members of the staff who personally attended the defendant such as to justify his making a personal charge for their services. He was not their employer nor was the hospital a private one, owned and operated by him. Hence he could have only a personal and individual claim against the defendant if he had personally rendered him some service, but, as the evidence showed, he had never personally attended him. The judgment for the plaintiff was therefore reversed.—*Pfeiffer v. Krohe, 11 A. (2d) 555 (Penna., 1940).*

**Charitable Hospitals: Liability for Tort When Covered by Insurance.**—The defendant charitable hospital was insured against all liability for the torts of its agents in the conduct of its business. In a suit against the hospital for damages for negligence in the care and treatment of a pay patient, the specific question for determination was whether a charitable institution is immune from tort liability even though a judgment against it would not jeopardize the trust fund but would be limited to funds derived from indemnity insurance. The Supreme Court of Colorado, in reversing a judgment for the defendant hospital, held, as it had held in prior cases, that the trust fund rule did not bar a judgment against a charitable institution but barred only a levy of execution against any property which was a part of the charitable trust. The fact that the defendant had insurance, therefore, merely made a judgment collectible but neither increased nor diminished the liability itself.—*O'Connor v. Boulder Colorado Sanitarium Ass'n, 96 P. (2d) 835 (Colo., 1939).*

## Society Proceedings

### COMING MEETINGS

Annual Congress on Medical Education and Licensure, Chicago, Feb. 17-18. Dr. W. D. Cutter, 535 North Dearborn St., Chicago, Secretary.

American Orthopsychiatric Association, New York, Feb. 20-22. Dr. Norvelle C. La Mar, 149 East 73d Street, New York, Secretary.

Central Surgical Association, Ann Arbor, Mich., Feb. 28-March 1. Dr. George M. Curtis, Ohio State University, Columbus, Ohio, Secretary.

Mid-South Post-Graduate Medical Assembly, Memphis, Tenn., Feb. 11-14. Dr. A. F. Cooper, Goodwyn Institute Bldg., Memphis, Tenn., Secretary.

Pacific Coast Surgical Association, Los Angeles, Feb. 19-22. Dr. H. Glenn Bell, University of California Hospital, San Francisco, Secretary.

Society of University Surgeons, St. Louis, Feb. 14-15. Dr. Frank Glenn, 525 East 68th St., New York, Secretary.

Western Section, American Laryngological, Rhinological and Otological Society, San Francisco, Feb. 1-2. Dr. Robert C. Martin, 384 Post St., San Francisco, Chairman.

# Current Medical Literature

## AMERICAN

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Titles marked with an asterisk (*) are abstracted below.

### Alabama State Medical Assn. Journal, Montgomery

**10**:157-188 (Nov.) 1940

More Recent Ideas in Treatment of Burns. L. Noland and C. H. Wilson, Fairfield.—p. 157.
The Newborn as a Pediatric Entity. J. R. Garber, Birmingham.—p. 162.
Sulfanilamide and Its Derivatives. D. C. Haisten, Dothan.—p. 166.
Urinary Infections in Children. J. P. Robertson, Birmingham.—p. 170.

### American Journal of Cancer, New York

**39**:463-614 (Aug.) 1940

Endogenic Blastogenic Substances. H. E. Kleinenberg, S. A. Neufach and L. M. Shabad, Leningrad, Soviet Union.—p. 463.
Production of Benign and Malignant Skin Tumors in Mice Painted with Bantu Liver Extracts. M. J. A. des Ligneris, Johannesburg, South Africa.—p. 489.
Examination of Human Tissue for Carcinogenic Factors. I. Hieger, London, England.—p. 496.
Cytology of 1, 2, 5, 6-Dibenzanthracene Mouse Tumors. M. Levine and H. Bergmann, New York.—p. 504.
Chemical Compounds as Carcinogenic Agents: Second Supplementary Report: Literature of 1938 and 1939. J. W. Cook and E. L. Kennaway, Glasgow, Scotland.—p. 521.

### Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

**44**:645-804 (Nov.) 1940

Specialization Within Roentgenology. M. C. Sosman, Boston.—p. 645.
Some Aspects of Biologic Action of Ionizing Radiations. G. Failla, New York.—p. 649.
Adolescent Development of Sella Turcica and Frontal Sinus Based on Consecutive Roentgenograms. C. B. Davenport, Cold Spring Harbor, N. Y., and Olive Renfroe, Thiells, N. Y.—p. 665.
Use of Thorium Dioxide in Roentgenography of Sinuses. R. C. Grove and R. A. Cooke, New York.—p. 680.
*Acute Mediastinitis: Roentgenologic, Pathologic and Clinical Features and Principles of Operative Treatment. H. Neuhof and C. B. Rabin, New York.—p. 684.
Roentgenologic Differentiation of Rheumatic from Nonrheumatic Mitral Valve Calcifications. B. S. Epstein, Brooklyn.—p. 704.
*Prognosis in Silicosis. J. T. Farrell Jr., M. J. Sokoloff and R. Charr, Philadelphia.—p. 709.
Epihyal Bone: Consideration of Some Small Accessory Bones of Neck. W. A. Evans Jr., Detroit.—p. 714.
Leiomyosarcoma of Fundus of Stomach with Perforation. M. Mass and J. D. Kirshbaum, Chicago.—p. 716.
Persistence of Notochord. G. R. Krause, Cleveland.—p. 719.
Fractures of Spine After Metrazol Convulsive Therapy and Other Convulsive States. M. M. Pearson and H. W. Ostrum, Philadelphia.—p. 726.
Study of Bone Metastases from Carcinoma of Prostate. J. H. Marks, Boston.—p. 732.
Radium Treatment of Rodent Ulcer Near Eye. A. A. Charteris, Glasgow, Scotland.—p. 737.
Radium Treatment of Vascular Nevi: Analysis of 152 Cases Seen During 1928-1938. E. A. Pohle and J. B. McAneny, Madison, Wis.—p. 747.
Effect of Roentgen Irradiation on Lymphatic Transport of India Ink. E. D. Sugarbaker and K. Sugiura, New York.—p. 756.

**Acute Mediastinitis.**—Neuhof and Rabin collected 67 cases from the records of the Mount Sinai Hospital for a period of ten years. Acute infections of the pharynx and injuries to the esophagus accounted for more than three fourths of the cases. In acute mediastinal lymphadenitis no abnormalities, as a rule, are discernible on the film. When the nodes are greatly enlarged they may cause a widening of the mediastinal shadow. Occasionally the enlarged paratracheal nodes may be observed as discrete shadows. A marked widening of the superior mediastinal shadow with bulging borders, simulating an expanding abscess, may be caused by large suppurating mediastinal lymph nodes which are matted together. Roentgenograms in oblique position may occasionally disclose inflamed lymph nodes. Roentgenograms in the early stages of phlegmonous mediastinitis may not disclose any abnormality. In most cases there is a diffuse widening of the superior mediastinal shadow. In suspected cases, films of the neck in the lateral position, a widened retrotracheal (prevertebral) shadow may infer the diagnosis. The earliest stages of abscess of the upper mediastinum may simulate phlegmonous mediastinitis, but the rapid widening of the shadow and a bulging border usually establish the diagnosis. An abscess of the lower mediastinum that extends to the right side causes a semicircular shadow to project into the right pulmonary field. An abscess which extends to the left may be overlooked because of its relation to the heart. In mediastinal abscess with perforation of the esophagus a widened mediastinal shadow following an accident capable of causing esophageal perforation is presumptive evidence. Similarly roentgen evidence of mediastinal or subcutaneous emphysema following such an injury is indirectly indicative. The early picture of a mediastinal abscess perforating into the lung is that of a localized area of pneumonic consolidation adjacent to the mediastinum. The fulminating cases presented the rare textbook picture of overwhelming sepsis or, more commonly, dysphagia, dyspnea and later severe "pneumonia." Throat infection with or without a retropharyngeal abscess or esophageal trauma was the etiologic factor. Cases of moderate severity either of nontraumatic or of traumatic origin were fatal when the source was nonsuppurative or, if suppurative, when the causative abscess had not been evacuated adequately. The duration was from a week to a month or longer. Beginning with sore throat, fever and chill in the nontraumatic group, and with pain in the neck and chest, dysphagia and fever in the traumatic, the course in both was characterized by moderate toxemia and dysphagia. A deceptive remission occurred in the fatal cases. The relatively mild cases presented a suppurative mediastinal lesion, usually a well localized abscess. In all cases an abscess in the cervical region had been present, and fever had continued without a discernible local cause after the cervical abscess had been drained. Dyspnea, cough or pain called attention to an intrathoracic complication. Clinical manifestations referable to the mediastinal infection are not always present. Physical examination of the chest is essentially negative in most instances of acute mediastinal infection except when signs of pleural effusion or pneumonic infiltration exist. Spinal percussion tenderness is a suggestive sign. Infiltration and tenderness are often present following trauma to the cervical esophagus. The trachea is displaced forward when a mediastinal infection is derived from an infection deeply situated in the lower cervical region. The most important operative indication is prophylactic and is concerned with the lesion which frequently precedes the mediastinal infection. Exposure of and drainage to the laceration in the esophagus is indicated in most cases. Cervical infection of nontraumatic origin was the source of mediastinal infection in about one third of their cases. Adequate and timely drainage would have obviated some. The site of the collection of pus in the neck should determine the entry to the mediastinum. Drainage of the latter via the neck may possibly be adequate down to the fourth dorsal vertebra but will not be adequate below this level. A posterior mediastinotomy should be added when further descent is suspected. Exploratory puncture is probably a questionable procedure. The roentgenogram is the basic guide for correct approach to the mediastinal abscess, and no positions should be omitted from which information as to the exact site of the lesion may be obtained.

**Prognosis in Silicosis.**—Farrell and his colleagues discuss the factors which influence the prognosis of silicosis. In their study of 511 anthracite coal miners with silicosis they found that only 77 were discharged as improved, 243 as unimproved and 191 died. The ages of those who improved and those who died varied from 15 to 69 years. Most of the deaths occurred in the fifth and sixth decades and were among those who had worked from eighteen to twenty-three years. Emphysema was the most common complication and, when extensive, prognosis was unfavorable. The second most common complication was tuberculosis. The prognosis in the first and second stages of silicosis complicated by tuberculosis was the same as in nonsilicotic tuberculosis, but in stage 3 it was much worse. Patients with clinical tuberculosis but with negative sputum have a better prognosis than those with clinical tuberculosis and positive sputum. The roentgen changes most suggestive of tuberculosis were asymmetrical consolidation and cavitation, regardless of

the findings in the sputum. Lobar pneumonia terminated fatally more often in patients with silicosis than in nonsilicotic patients. Heart disease, a common accompaniment of silicosis, had a characteristic clinical course and made the prognosis unfavorable. The most common type was myocardial degeneration. Miners with clinical symptoms of myocardial disease and roentgen evidence of cardiac enlargement without symptoms and toxemia usually suffered cardiac deaths. Those with clinical and roentgen signs of heart disease but with marked toxic symptoms of tuberculosis usually died of the latter disease. Spontaneous pneumothorax occurred more frequently in silicosis complicated or uncomplicated by tuberculosis than in any other pulmonary disease; it was present in 22 instances. It may be bilateral and affects the prognosis unfavorably. Carcinoma of the bronchus, not a common complication, makes the prognosis hopeless.

## Am. J. Syphilis, Gonorrhea and Ven. Dis., St. Louis

**24**:671-822 (Nov.) 1940

Methods for Isolation and Cultivation of Treponemes, with Special Reference to Culture Mediums. Clara C. Kast and J. A. Kolmer, Philadelphia.—p. 671.
Interpretation of Bruusgaard's Paper on Fate of Untreated Syphilitics. W. T. Sowder, Baltimore.—p. 684.
Long-Term Results in Treatment of Early Syphilis. P. Padget, Baltimore.—p. 692.
Cooperative Plan for Rapid Appraisal of Chemotherapy of Gonorrhea in the Male. O. F. Cox and J. H. Watkins, Boston.—p. 732.
Nile Blue a Medium for Culture of Gonococcus. L. W. Gardner, Detroit.—p. 737.
Present Day Treatment of Gonorrhea with Fever Therapy. A. I. Mann, Los Angeles.—p. 743.
Antisyphilitic Treatment Administered by a Layman to Himself. J. L. Callaway, Durham, N. C.—p. 745.
Transverse Diffuse Myelitis of Spinal Cord Following Intravenous Neoarsphenamine: Report of Case Showing the Jarisch-Herxheimer Reaction. V. Moseley and J. L. Callaway, Durham, N. C.—p. 746.
How Do the Officially Recognized Serologic Tests for Syphilis Rank in Specificity and Sensitivity? N. Nagle, St. Louis.—p. 750.
Late Congenital Syphilis: Observations on Thirty-Nine Patients Over 25 Years of Age at Time of First Admission. F. R. Smith Jr., Baltimore.—p. 755.
Outline of History of Syphilis. J. E. Kemp, Chicago.—p. 759.
Microbiology of Syphilis: Present Status. J. S. Snow, Ann Arbor, Mich.—p. 780.

## American Review of Tuberculosis, New York

**42**:699-838 (Dec.) 1940

*Disappearance of Tubercle in Pulmonary Tuberculosis: Tuberculo-Asepsis. J. M. MacMillan, Rochester, N. Y.—p. 699.
Pathology of Clinically Healed Tuberculous Cavities. O. Auerbach and H. Green, Staten Island, N. Y.—p. 707.
Healing of Tuberculous Cavities. M. Pinner, New York.—p. 731.
Angular Roentgenography of Pulmonary Apex. L. Ramo and M. J. Lustok, with technical assistance of Leone W. Stroud, Spivak, Colo.—p. 738.
*Tuberculous Empyema: Critical Review of 112 Consecutive Cases. J. H. Skavlem, M. L. Phelps, L. E. Baker and J. N. Christiansen, Cincinnati.—p. 747.
Pathogenesis and Localization of Pulmonary Tuberculosis. B. L. Brock, Waverley Hills, Ky.—p. 755.
Tuberculosis of Tongue: Report of Nine Cases. J. E. Farber, E. Friedland and W. F. Jacobs, Buffalo.—p. 766.
Hoarseness in Tuberculosis. W. F. Hulse, Cleveland.—p. 776.
Growth of Tubercle Bacilli in Tissues of Normal and Allergic Guinea Pigs. C. E. Woodruff and Ruby Green Kelly, Northville, Mich.—p. 782.
Bacteriologic Diagnosis of Tuberculosis: Further Comparisons of Efficiency of Smear, Culture and Guinea Pig Inoculation in Detection of Tubercle Bacillus in Clinical Practice. H. G. Whitehead, with technical assistance of Dorothea Hilgeman, Baltimore.—p. 795.
Sulfapyridine in Experimental Tuberculosis in Guinea Pigs. F. H. Heise and W. Steenken Jr., Trudeau, N. Y.—p. 801.

**Disappearance of Tubercle in Pulmonary Tuberculosis.**—MacMillan presents 3 illustrative cases of a large group who had active pulmonary tuberculosis, became inactive through treatment and died from causes other than macroscopic or microscopic tuberculosis. Such self-limiting pulmonary tuberculosis he terms pulmonary tuberculo-asepsis. He believes that the complete absence of tuberculosis at necropsy in proved cases has not been thoroughly correlated and sufficiently emphasized by clinicians and pathologists. In the 3 illustrative cases extensive and active pulmonary tuberculosis with positive sputum had at one time been present. Their clinical pictures, varying slightly in the individual case, show the symptomatology usually associated with active disease. For years they were sputum negative and at postmortem examination, outside of fibrosis, calcification, bronchiectasis and emphysema, were classified by pathologists as not presenting classic tuberculosis. None of the usual gross or microscopic pathologic signs of tubercle formation were discovered. Tuberculosis going on to asepsis places the disease on a basis similar to other infectious diseases. The author feels that this fact is the rule and not the exception. Generally, emphysema, bronchiectasis, fibrosis and calcification, alone or in any combination, may be the only roentgen or pathologic sign of pulmonary disease. The appreciation of these observations should always include the possibility of tuberculosis being the original etiologic factor. It is the routine at the Iola Sanatorium, when such a possible case presents itself, to take a detailed history. The most frequent symptom leading to the detection of this type of case has been pulmonary hemorrhage in apparently well individuals. This usually follows some severe respiratory infection such as suppurative bronchitis, but calcification must not be forgotten. Chronic cough and sputum of many years' duration may be present, but these symptoms are usually minimized or denied although roentgenograms of the chest reveal extensive pulmonary disease. Associated symptoms (cough, sputum and dyspnea) must be studied extensively and evaluated properly. In the foreground one may note an unusual efficiency of alveolar phagocytosis, pulmonary hemorrhage or cor pulmonale, alone or in combination, as determining factors of this entity, and these warrant further study.

**Tuberculous Empyema.**—Skavlem and his associates studied 112 consecutive cases of tuberculous empyema encountered during four years at the Hamilton County Tuberculosis Hospital in Cincinnati. Parenchymal pulmonary lesions were demonstrated either by roentgenograms or by tubercle bacilli in the sputum in practically all of the cases. In a few cases empyema followed a simple pleurisy with effusion, the fluid originally being clear. During the period (1936 to 1939 inclusive) under study 898 cases of therapeutic pneumothorax were observed; empyema subsequent to the institution of the treatment developed in 94. A few cases were discovered only at necropsy. Tuberculous empyema, like pulmonary tuberculosis, is a disease of the young (66 patients from 15 to 30 years of age) and middle aged (43 from 31 to 50 years of age). Only 3 patients were more than 50 years of age. There was a decidedly higher percentage of males (78 cases) than females (34 cases). A larger percentage of male patients are admitted to the institution in the far advanced stage of pulmonary tuberculosis than female patients. Tuberculous empyema occurs more frequently in Negro patients than in white patients. The types of pulmonary lesions have been divided into chronic fibroid (22), chronic fibroid with caseous bronchopneumonia (59) and exudative (31), which is more common in the Negro. The location of the lesions seemed to have no great significance, except that many of the exudative lesions involved the basal part or the entire lung. The most frequent complication of tuberculous empyema was bronchopleural fistula, then chest wall sinus and then secondary pleural infection. Treatment was indifferent (bed rest, opiates and occasional thoracentesis), oleothorax and surgical intervention. Of the 41 patients receiving indifferent treatment, 40 died in the hospital and the remaining 1 signed out and the result is unknown. Fourteen of the 40 patients treated by oleothorax died and of the 13 patients who apparently recovered and were discharged it was often found that the lung on the affected side had completely or almost completely reexpanded. The authors believe that patients with this type of involvement owe their recovery to the obliteration of the infected pleural space by reexpansion rather than to any particular bactericidal qualities of the gomenol (aromatized oil). The remaining 13 patients are still in the institution; most of them are improved. Many of this group are Negro men whose exercise is greatly limited. The results of surgical intervention are encouraging. Of 24 patients treated by thoracoplasty 14 have recovered, 3 have died (2 of whom were very poor operative risks) and 7 are still under treatment, but all are improved with every prospect of recovery. Seven patients with secondary infection were treated by thoracotomy; 5 of them have died and 2 are still in the hospital with an uncertain future. It is dangerous to delay treatment until bronchopleural fistula and secondary infection develop. The high mortality among the patients treated indifferently demonstrates the futility of not aiding the efforts of nature. The

most satisfactory treatment appears to be extrapleural thoracoplasty. Preoperative preparation of these patients with 5 per cent gomenol in olive oil in the pleural cavity has been found beneficial.

## Annals of Surgery, Philadelphia

**112**:977-1146 (Dec.) 1940

Carcinoma of Thyroid. F. H. Lahey, H. F. Hare and S. Warren, Boston.—p. 977.
Studies Relating to Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis. J. D. Bisgard and C. P. Baker, Omaha.—p. 1006.
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## Archives of Neurology and Psychiatry, Chicago

**44**:1155-1372 (Dec.) 1940

*Inheritance of Cerebral Dysrhythmia and Epilepsy. W. G. Lennox, E. L. Gibbs and F. A. Gibbs, Boston.—p. 1155.
Neurologic Significance of Platybasia. W. A. Gustafson and E. Oldberg, Chicago.—p. 1184.
*Electroencephalograms of "Constitutionally Inferior" and Behavior Problem Children: Comparison with Those of Normal Children and Adults. D. B. Lindsley and Katharine Knox Cutts, East Providence, R. I.—p. 1199.
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Cerebral Changes in Rocky Mountain Spotted Fever. G. B. Hassin, Chicago.—p. 1290.
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Treatment of Trigeminal Neuralgia with Vitamin $B_1$ (Thiamine Hydrochloride). A. S. Rose and B. M. Jacobson, Boston.—p. 1307.
Element of Optical Illusion in Appearance of Preservation of Axis Cylinders in Certain Lesions of Central Nervous System. L. Alexander, Boston, and T. J. Putnam, New York.—p. 1312.

**Inheritance of Cerebral Dysrhythmia and Epilepsy.**—Three years ago Lennox and his colleagues began to study the electroencephalographic tracings of 183 near relatives of 94 epileptic patients with cerebral dysrhythmia. The most conclusive evidence supporting the hypothesis that the electroencephalogram is of genetic value is found in the records of similar twins. Tracings from 9 pairs of normal identical twins previously secured by the Davises as well as the authors' records of 7 pairs who had some physical or neurologic abnormality are available. Six pairs of the authors' twins also had cortical dysrhythmia. In each of the 16 pairs the 2 members had similar tracings, whether the tracings were normal or abnormal. Neurologic and electroencephalographic differences existed in the records of 2 pairs of twins. This was due to an acquired cerebral lesion in 1 twin, but a similarity in the basic cortical rhythms was still present. Of the 94 patients examined, the electrical records of 4 were not secured and the records of 2 were normal. One of the patients with normal records had had only a few convulsions and the other had been free from symptoms for seventeen years. Of the relatives tested 143 were parents, 36 were siblings and 4 were children. Tracings were made simultaneously from six areas of the cortex. Definitely abnormal records were obtained in 60 per cent of the relatives and in 10 per cent of a control group of 100 persons who had no near relative with epilepsy. In 55 families records were obtained from both parents and 35 per cent of the records of both parents were abnormal. In only 5 per cent were the records of both parents unmistakably normal. Dysrhythmia was as frequent among the relatives of patients with so-called symptomatic epilepsy as among the relatives of patients with "essential" epilepsy. It occurred more often among the relatives of female (64 per cent) than of male patients (56 per cent) and more often among female relatives (65 per cent) than among male relatives (54 per cent). The data include 5 families with similar twins with seizures or dysrhythmia. In each pair of twins there was a similarity of the fundamental rhythm, though the twins of only 1 pair had seizures. The authors believe this evidence indicates that the dysrhythmia of epilepsy is inheritable and that such a dysrhythmia may represent a predisposition to epilepsy or some allied disorder. Dysrhythmia may prove to be a dominant trait. Approximately 2.4 per cent of the near relatives of noninstitutionalized patients have a history of seizures and approximately 60 per cent of relatives have dysrhythmia; therefore the authors point out that numerically persons with the predisposition to epilepsy or an allied disorder outnumber actual epileptic subjects by about 25:1. The incidence of epilepsy in the population is about 0.5 per cent; hence persons with a predisposition to epilepsy form about 12 per cent of the population. These observations should be of practical value in the prophylaxis and eugenics of epilepsy by assisting the physician in tracing the descent of epilepsy and in advising patients and their relatives about marriage. Dysrhythmia in both parents was thirty-five times greater than the expected chance mating of two dysrhythmic persons. If a person with epilepsy marries, his chances of having epileptic offspring will be minimized if he chooses a person whose cortical electrical activity is normal. The eugenic possibilities of the subject are of great importance to the nation and the individual.

**Electroencephalograms of Physically Inferior and Problem Children.**—Lindsley and Cutts present evidence which demonstrates that the electroencephalogram of a normal subject differs significantly from that of behavior problem and "constitutionally inferior" children. The studies were made on 36 apparently normal and healthy children from 7 to 13 years of age, 30 apparently healthy college students of superior intelligence, 50 behavior problem children from 7 to 13 years of age and 22 "constitutionally inferior" children from 7 to 13 years of age. The "constitutionally inferior" children had in general a very poor biologic, social, economic and medical heritage. They were all wards of the state and most of them were unplaceable by social agencies in foster homes. They were of dull normal or very low average mental ability, having an average intelligence quotient of 88. Simultaneous electroencephalographic recordings from four regions (right occipital, parietal, frontal and central) of the head were made of all four groups of subjects. None of the 30 college students had rhythms within 2 to 5 per second in the occipital or frontal region and only 1 showed such a rhythm in the central region. There were some children in all three groups with rhythms of this frequency; the behavior problem children were approximately twice as frequent with such rhythms as the normal or the "constitutionally inferior." For example, in the central region 52 per cent of the behavior problem children had from 2 to 5 per second waves whereas only 25 per cent of the normal group and 23 per cent of the "constitutionally inferior" group showed such rhythms. The average frequency of these rhythms was essentially the same in all groups, but the average amplitude and percentage of time were higher among the behavior problem children. The subjects with rhythms from 5 to 8 per second were from two to three times as great in the behavior problem and "constitutionally inferior" groups as in the normal groups. The average amplitude and percentage of time were also slightly greater in the former than in the latter groups. There were no significant differences in average frequency among the groups. There were no differences in the average frequency of the alpha waves (from 8 to 12 per second) among the three groups of children, but the behavior problem

and "constitutionally inferior" children had a higher average amplitude. The adult group had a higher average frequency and a lower average amplitude than the children. The percentage of time measurements for all groups ranged from 72 to 78 in the occipital, 39 to 47 in the central and 21 to 24 in the frontal region. Only a small percentage of subjects in any of the groups showed rhythms within the range of from 12 to 18 per second. There were no significant differences among the groups except that the frequency was higher among the adults. The so-called beta band (from 18 to 30 per second) showed approximately the same average frequency and range in all the groups but a lower maximal amplitude among the adults. From the data it is apparent that the higher frequency bands, from 8 to 12, 12 to 18 and 18 to 30 per second, are of no value in differentiating the three groups of children. However, there were important differences among the groups in the low frequency bands. The normal adult group showed little evidence of the 5 to 8 per second rhythms and almost complete absence of the 2 to 5 per second rhythms. The slow rhythms when present were found more frequently in the central than in the occipital or frontal region. The authors discuss the differences in the amount of abnormal slow waves among the various groups and suggest that such disturbances of cortical function are probably important factors in behavior disorders.

## Archives of Ophthalmology, Chicago

**24**:1077-1306 (Dec.) 1940

Classification of Ocular Pathology. A. B. Reese, New York.—p. 1077.
Sclerocorneal Trephining (Elliot's Operation). W. L. Benedict, Rochester, Minn.—p. 1100.
What Is the Minimal Routine Examination of Muscles? J. W. White, New York.—p. 1113.
Vascular Basis of Uveal Disease: Acute Anoxia as Fundamental Pathologic Physiology. W. F. Duggan, Utica, N. Y.—p. 1123.
*Myopia After Use of Sulfanilamide. E. A. Rittenhouse, McKeesport, Pa.—p. 1139.
Regeneration of the Aqueous. J. G. Bellows and H. Chinn, Chicago.—p. 1144.
Experimental Exophthalmos and Associated Myopathy Induced by Thyrotropic Extract. R. B. Aird, San Francisco.—p. 1167.
Repeatability of Ophthalmoeikonometer Measurements. K. N. Ogle, H. A. Imus, L. F. Madigan, R. E. Bannon and E. C. Wilson, Hanover, N. H.—p. 1179.
Cirsoid Aneurysm of Orbit; Report of Two Cases. H. R. Sniderman, Toronto, Canada.—p. 1190.
*Primary Pituitary Adenoma and Syndrome of Cavernous Sinus: Clinical and Anatomic Study. L. M. Weinberger, F. H. Adler and F. C. Grant, Philadelphia.—p. 1197.
Carcinoma of Lacrimal Sac: Report of Second Case. C. N. Spratt, Minneapolis.—p. 1237.
Unusual Changes in Lens Following Trauma: Origin and Treatment. D. M. Rolett, New York.—p. 1244.

**Myopia After Sulfanilamide.**—Rittenhouse reports a case of transitory myopia following sulfanilamide therapy and states that literature contains 6 other cases. One must determine whether the myopia was caused by the infection or by the drug or whether it is coincidental. He believes that lenticular changes probably best explain the myopia. It is conceivable that the rapid absorption of the drug can affect a transformation of the salt and water metabolism and thus cause a change in the lens which would be responsible for the refractive disturbances. Toxic irritation of the parasympathetic fibers of the ciliary muscles must be considered. Sensitivity to the drug may be possible as most of the patients affected at first used the drug with impunity with the trouble developing at the next administration. Although the actual mechanism is not known, the rapid onset of the myopia after taking the drug and the apparent recovery after its discontinuance seem to indict sulfanilamide. A good prognosis with no apparent ill after-effects is reassuring.

**Primary Pituitary Adenoma and Cavernous Sinus Syndrome.**—Weinberger and his co-workers state that literature indicates that paralysis of the ocular nerves is not rare in cases of pituitary adenoma but that there is no adequate discussion of its significance when associated with pituitary tumor, the mechanism of its production, the anatomic arrangement which permits it to occur, its diagnostic or prognostic importance or its surgical implications. A study of the 169 cases of pituitary adenoma collected from the Hospital of the University of Pennsylvania disclosed 14 in which paralysis of the ocular nerves dominated the clinical picture and in some comprised the exclusive complaint and neurologic observation. The group, though showing individual clinical variations, presented a fairly consistent neurologic pattern. The cases are described to draw attention to the effect of pituitary adenoma on the ocular nerves and structures in the cavernous sinus. The cases are divided into groups: Group 1 consists of those in which paralysis of the ocular nerve and trigeminal nerve disturbances were the first and exclusive complaints without impairment of visual function. In group 2 involvement of the structures of the cavernous sinus dominated the clinical picture, although examination disclosed variable degrees of injury to the optic nerves and chiasm. Group 3 cases presented ample evidence of chiasmal injury and the diagnosis of pituitary adenoma was not difficult. The structures contained in the cavernous sinus were involved so that the main clinical symptoms were referred to these structures. Disturbances referable to the ocular and trigeminal nerves played an important role in the symptoms, but evidence of injury to the optic chiasm and optic nerves was compatible with an intrasellar lesion. Although there were many differences among the foregoing cases, there was a basic similarity referable to involvement of the structures in the cavernous sinus. It was shown that occasionally pituitary adenomas grow laterally and that this mode of growth may produce the clinical picture of a lesion in the sphenoid fissure rather than the classic chiasmal syndrome. Radiation seems to relieve the symptoms caused by involvement of the nerves contained in the cavernous sinus. Palsy of the ocular nerves disappeared in 2 cases after roentgen treatment. Surgical extirpation when the tumor has escaped from the sella turcica is difficult and dangerous. Roentgen therapy as a primary treatment for pituitary adenomas should be reconsidered in this light. If roentgen therapy is used first and is unsuccessful, the tumor may spread widely, thus making a surgical attack difficult and hopeless if occasion demands it later on.

## Georgia Medical Association Journal, Atlanta

**29**:519-562 (Nov.) 1940

Presentation of the President's Key to Dr. William H. Myers, of Savannah. A. H. Bunce, Atlanta.—p. 519.
Progress in Knowledge and Control of Cancer. K. M. Lynch, Charleston, S. C.—p. 521.
Status and Function of the Industrial Physician. L. Noland, Fairfield, Ala.—p. 525.
Hypometabolism and Myxedema. M. V. B. Teem, Marietta.—p. 528.
Imperforate Hymen with Hematocolpos: Report of Case. G. A. Holloway, Atlanta.—p. 535.
Tuberculosis of Bone. H. W. Jernigan, Atlanta.—p. 537.
A Layman Looks at the Family Doctor. Helen Estes, Gainesville.—p. 540.

## Kansas Medical Society Journal, Topeka

**41**:453-496 (Nov.) 1940

The Physician's Responsibility in Industrial Work. E. Wyman, Topeka.—p. 453.
Ocular Symptoms and Signs in Certain General Diseases. C. S. O'Brien, Iowa City.—p. 456.
Management of Perforated Appendix. E. R. Gelvin, Concordia.—p. 460.
Cleidocranial Dysostosis: Survey of Six New Cases and 126 from Literature. P. W. Miles, Kansas City.—p. 462.
Carcinoma of Cecum Simulating Appendicitis. J. B. Stoll, Clay Center.—p. 468.
Carcinoma of Fallopian Tube: Report of Two Cases. M. A. Walker and H. H. Hesser, Kansas City.—p. 469.

## Review of Gastroenterology, New York

**7**:457-550 (Nov.-Dec.) 1940

Early Experiences in Flexible Gastroscopy. G. McNeer, New York.—p. 457.
Gastroscopy with Statistical Report of 100 Patients. J. M. Rumball, Pittsburgh.—p. 463.
Combined Treatment of Gastroduodenal Ulcer. C. A. Brusch and J. A. Brusch, Cambridge, Mass.—p. 471.
Pain Mechanism in Peptic Ulcer and Pseudo-Ulcer Syndrome: Control of These Disorders with Low Carbohydrate Diet. B. P. Sandler, New York.—p. 485.
Cooperative and Coordinate Gastroenterologic and Surgical Problems. I. Cohn, New Orleans.—p. 500.
Chronic Ulcerative Colitis: Deficiency States. I. R. Jankelson and C. W. McClure, Boston.—p. 506.
Interpretation of Low Metabolism in Gastroenterologic Practice. M. Golob, New York.—p. 512.
Vitamin K: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas. H. P. Smith and C. A. Owen, Iowa City.—p. 520.
Hyperglycemic Shock. C. L. Glaessner, New York.—p. 528.

## FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

### British Journal of Surgery, Bristol

**28**:161-336 (Oct.) 1940

Carotid Tumors. G. Gordon-Taylor.—p. 163.
Concerning the Origin and Nature of Certain Malformations of Face, Head and Foot. A. Keith.—p. 173.
Sacroiliac Tuberculosis. H. J. Seddon and F. G. St. C. Strange.—p. 193.
Nature and Cause of Swelling of Upper Limb After Radical Mastectomy. E. A. Devenish and W. H. G. Jessop.—p. 222.
Volkmann's Ischemic Contracture. D. L. Griffiths.—p. 239.
*Treatment, Complications and Late Results of Acute Hematogenic Osteomyelitis: Based on Study of 500 Cases Admitted to the London Hospital During the Years 1919-1937. E. C. B. Butler.—p. 261.
Nonmalignant Stricture of Esophagus: Two Cases. G. G. Turner.—p. 275.
Leiomyomas of Stomach. H. Edwards and E. E. Lewis.—p. 284.
Spread of Acute Intraperitoneal Effusions. G. A. G. Mitchell.—p. 291.
Supernumerary and Ectopic Ureters: Carcinoma of Double Kidney, with Ectopia of One Ureter. G. H. Baines.—p. 314.
Resection of Growths of Lower Pelvic Colon: New Method of Anastomosis. S. Pringle.—p. 320.
Emphysema of Biliary Passages. P. H. Whitaker and J. P. Steel.—p. 325.

**Acute Hematogenic Osteomyelitis.**—Butler states that acute osteomyelitis is a diminishing disease in the East End of London as, between 1919 and 1928, 344 cases were admitted but from 1929 to 1937 there were only 156 admissions. He attributes this decrease to the better health and home conditions which now prevail; no other cause was evident. There was a higher incidence in males (67 per cent) as compared to females (33 per cent). This is attributed to the more adventurous life and greater exposure to trauma of the male population. The disease was most prevalent up to the age of 20 among both sexes. There was a history of injury in 43 per cent of cases. In no case did osteomyelitis supervene on a simple fracture. A primary septic focus was present in 93 cases. However, the importance of a septic focus was not realized in the past, and its presence or absence was rarely placed on record. More recently a much higher percentage has been found. There were 127 deaths. The rate has been the same for the two sexes. The death rate has remained constant despite the decreased incidence and conservative treatment of recent years. Of the 500 patients, 469 were operated on on admission or shortly after. The death rate of the three main types of operation (drainage of a periosteal abscess, periosteal incision and osseous drilling and drainage of a medullary cavity) were the same, 21 per cent. Immediate amputation saved the lives of 2 patients on whom it was performed, but they both died later from recurrent infections in other bones and pyemia. This suggests that amputation should not be performed until the patient has acquired a real or artificial immunity against the staphylococcus. Twenty-six of the 31 patients who had no operation either had fulminating bacteremia or the diagnosis was made only in the postmortem room. This group accounted for 22 per cent of the deaths. It is unlikely that even early surgery would have benefited them, as the bacteremia was the cause of their deaths. The incidence of sequestrectomy was lowest after drilling the bone. It is reasonable that the lessening of intramedullary tension followed by complete rest in plaster limited osseous destruction. Pathologic dislocation occurred once in the knee and four times in the hip. These late manifestations were not fatal. The fractures united except possibly one which could not be traced. The musculospiral nerves of 4 patients were affected, as were the external popliteal of 2 and the posterior interosseus of 2. All were postoperative lesions. One musculospiral lesion was treated with secondary suture and did well. The external popliteal lesions were permanent; recovery occurred in the others without surgical intervention. There were 124 instances of acute arthritis. Its effect on the immediate prognosis was moderate. However, it did have a bad effect on the ultimate function of the limb. Only 37 per cent of these patients who left the hospital had a movable joint. Of the 500 patients 373 lived and of these it was possible to trace 223; 160 were examined in the follow-up department, 50 answered a questionnaire and 13 had died, giving a late mortality of 3.5 per cent. Of 137 patients observed after ten or more years 121 were at work, 65 had a good result, 58 required recurrent operation, 22 had a recurrent discharge, 32 had recurrent pain and 48 had some deformity. Of 39 patients seen between five and ten years later the respective figures are 36, 20, 18, 8, 7 and 9, and likewise for the 47 admitted during the last four years of the study the figures are 38, 25, 11, 15, 6 and 16. Forty-four of the three groups of patients required operations on other bones, 36, 4 and 4 cases in each respective group. The author's criteria for a good clinical result is a completely healed wound, no deformity of bone or limb apart from a scar and no recent active focus in any part of the body. The surgical treatment of a serious case of osteomyelitis should have the active cooperation of a bacteriologist and a surgeon. The high mortality of this and other acute staphylococcic infections may in this way be reduced eventually.

### British Journal of Tuberculosis, London

**34**:81-140 (July-Oct.) 1940

Rounding Out the Tuberculosis Campaign. L. I. Dublin.—p. 84.
Rehabilitation. P. Varrier-Jones.—p. 91.
Mental Disturbance in Pulmonary Tuberculosis. R. Y. Keers.—p. 100.
*Cod Liver Oil as Local Treatment for Tuberculous Lesions. A. L. Banyai.—p. 107.
Naturally Occurring Tuberculosis in Dogs and Some Other Species of Animals. R. Lovell and E. G. White.—p. 117.
Treatment of Tuberculosis of Larynx by Injection. J. R. Roberts.—p. 133.

**Cod Liver Oil Locally for Tuberculous Lesions.**—Banyai reports 164 cases of laryngeal and pharyngeal tuberculosis treated at the Muirdale Sanatorium by the topical application of cod liver oil by spray. Therapeutic effect was studied in 91. All the patients had active pulmonary tuberculosis. The laryngeal lesions were characteristic of tuberculosis associated with a chronic pulmonary process. Relief from disagreeable symptoms was prompt among those patients who responded favorably to the treatment. Several of the ulcer patients who used cocaine spray, anesthesin or euphagin tablets before the treatment were able to discontinue their use shortly after the cod liver oil treatment was begun. The disappearance of dryness, tickling and burning sensation in the throat, the cessation of pain localized to the larynx or radiated to the ear were frequently observed. With the elimination of the pain, dysphagia was relieved and the patient's nutrition and general well-being improved. Also cough diminished and expectoration became easier, permitting more pulmonary and general rest and sleep. Hoarseness disappeared, and the voice was restored to normal. A more optimistic mental attitude on the part of the patient followed these favorable changes. The improvement in the laryngeal lesions was striking as treatment progressed. Ulcers showed a rapid epithelization and healing that was comparable with the results seen in pharyngeal cases, provided the treatment was carried out consistently and well tolerated by the patient. A good therapeutic response was had by patients with various degrees of vegetative granulation. Other manifestations of the disease cleared up also satisfactorily. The patients with marked edema obtained the least effect, with complete failure in several. After treatment was continued from two months to one and a half years the lesions of 24 patients remained unimproved (8 died during the course of treatment), 42 improved subjectively and objectively and the lesions of 25 healed. The tuberculous empyema of 17 patients with no bronchopleural fistulas responded favorably to aspiration of the pus and to its replacement by small amounts of cod liver oil. No local or general reactions were observed. The purulent pleural exudate of 2 patients was reduced to a minimum and thus they became eligible for thoracoplasty for obliterating the infected, gaping pleural cavity. When marked general debility or amyloidosis was present, cod liver oil therapy failed. Cod liver oil aided the formation of healthy granulation, reduced purulent secretion and accelerated epithelization in operative wounds with a delayed tendency to heal. The oil was also of benefit in suppurating tuberculous lymph nodes (when seen early), phlyctenular conjunctivitis, keratoconjunctivitis, cold abscess secondary to bone tuberculosis, fistulas originating from tuberculous epididymitis, ischiorectal fistulas and scrofuloderma.

## British Medical Journal, London

**2**:619-656 (Nov. 9) 1940

Interpretation of Lateral Radiographs of Chest, with Special Reference to Tuberculosis in Childhood. S. Engel and G. G. Kayne.—p. 619.
Adsorption of Early Products of Bovine Tubercle Bacilli in Rabbits by Anthracite Dust. S. L. Cummins.—p. 623.
Convulsive Cardiazol Therapy in Cardiovascular Disorders. R. Good.—p. 624.
*Benzyl Benzoate Treatment of Scabies. R. E. King.—p. 626.
One-Layer Operation for Inguinal Hernia. K. Black.—p. 627.

**Benzyl Benzoate Treatment of Scabies.**—Of the many sulfur-free remedies for scabies King found the benzyl benzoate method introduced by Kissmeyer to be the most efficacious. In a series of 100 cases of scabies occurring in a naval establishment, 80 per cent of which were infected and of longer duration than two weeks, treatment by one application of the benzyl benzoate lotion proved completely successful. There were no unpleasant after-effects, except a slight generalized burning sensation, which usually lasted for about fifteen minutes. In 3 cases of gross pyodermatitis from scabies infection of long duration the application was repeated after four days because of a recurrence of nocturnal itching. This resulted in the disappearance of all irritation, and the septic cutaneous condition responded to simple treatment. The lotion consists of equal parts of benzyl benzoate, denatured alcohol and soft soap. It is applied vigorously for five minutes with a pig-bristle shaving brush after a thorough scrubbing of the whole body with soft soap and a ten minute soak in a bath at 100 F. After the first application dries another one is applied, the clothes worn before treatment are resumed and twenty-four hours later a bath is taken and clean clothes are put on. The portions of skin showing severe pyogenic infection must be treated as energetically as the unabraded areas.

## Clinical Science, London

**4**:217-340 (Oct.) 1940

*Excretion of Pregnandiol and Corpus Luteum. C. L. Cope.—p. 217.
Venous Pulsation in Orbit. T. Lewis.—p. 243.
*Observations on Periarteritis Nodosa. R. T. Grant.—p. 245.
Adjustment of Bloodflow to Affected Limb in Arteriovenous Fistula. T. Lewis.—p. 277.
Pituitary-like Factors in Blood and Urine of Diabetic Patients and of Animals Treated with Pituitary Extracts. H. P. Himsworth and R. B. Kerr.—p. 287.
Somatic Simulating Visceral Pain. J. H. Kellgren.—p. 303.
Simplification of Evans Blue Method of Blood Volume Determination. C. R. Harington, E. E. Pochin and J. R. Squire.—p. 311.
Thyrotropic Hormone in Blood. H. B. Collard, F. H. Mills, F. F. Rundle and E. P. Sharpey-Schafer.—p. 323.
Instrument for Measuring Quantity of Blood and Its Degree of Oxygenation in Web of Hand. J. R. Squire.—p. 331.

**Excretion of Pregnandiol and Corpus Luteum.**—Cope presents clinical material which confirms the principal claims of Venning and Browne that pregnandiol is excreted in the urine only during corpus luteum activity. Excision of the corpus luteum during early pregnancy results in a rapid fall to zero of the pregnandiol excretion, which normally continues in increasing amounts to full term. Pregnandiol is excreted during the luteal phase of the menstrual cycle, falls to zero before bleeding commences and is absent from the urine during the first or preovulatory half of the cycle. In contrast to this, no such excretion of pregnandiol occurred over a period of several weeks in two women suffering from secondary amenorrhea in whom it was unlikely that ovulation was occurring. No pregnandiol was excreted during three excessive uterine bleedings of a woman with a diagnosis of nonovulatory bleeding. This provides additional evidence of the close association between corpus luteum activity and pregnandiol excretion. All this is compatible with the main thesis of Venning and Browne. It must be remembered, however, that activity of a corpus luteum in nonpregnant women is usually associated with a secretory type of endometrium. The fact that the corpus luteum of pregnancy may be removed at the second or even the first month without abortion has led to the assumption that under these conditions the chorionic villi take over the hormone producing function of the corpus luteum. Since this seems very probable, the author feels that the adoption of a similar endocrine function by the normal premenstrual secretory endometrium is not an impossibility. Injection of progesterone to women not excreting any pregnandiol caused a small but definite amount of the substance to appear in the urine. In view of this it is not justifiable to assume that the magnitude of pregnandiol excretion necessarily gives any quantitative indication of the rate of progesterone production by the corpus luteum. The state of the endometrium might prove an important factor in determining the percentage yield of pregnandiol from a given quantity of progesterone. However, pregnandiol excretion curves may reflect the state of the endometrium more closely than the activity of the corpus luteum. Until contrary evidence is had, it must be assumed that the observed pregnandiol excretion represents only a small proportion of the total endogenous progesterone production. Therefore it must be determined whether pregnandiol is the most important excretory product of endogenous progesterone. Available evidence does not reveal appreciable quantities of any substance in the urine other than pregnandiol glucuronide and allopregnandiol, probably also present as a glucuronide, which might be considered a breakdown product of progesterone metabolism. The author concludes that pregnandiol excretion is a qualitative indication of corpus luteum activity in the nonpregnant woman and that it probably indicates progesterone production in pregnant and nonpregnant women. He does not believe that the pregnandiol excretion rate provides any reliable estimate of the intensity of corpus luteum metabolism. The great discrepancy between the relatively large amounts of pregnandiol recovered after progesterone injection by Venning and Browne and the failure to recover any by Hamblen, Ashley and Baptist and by Stover and Pratt together with the author's intermediate recoveries suggests to him that other factors, at present undefined, are concerned in determining the pregnandiol excretion from a given quantity of progesterone. If this is probable after injected progesterone it may be equally probable for endogenous progesterone. He believes that hormone influences other than renal or hepatic and the metabolic state of the uterus and endometrium will prove to be important in progesterone metabolism and pregnandiol excretion. The assumption that pregnandiol excretion reflects quantitative variations in corpus luteum activity is unsupported by direct evidence.

**Periarteritis Nodosa.**—Grant reports 7 cases of periarteritis or polyarteritis nodosa and suggests that the condition is much less rare than is commonly thought, that it is not necessarily or even usually fatal and that it can be recognized at the bedside in a considerable proportion of cases. Of his 7 patients encountered since 1937 only 3 have died. The diagnosis was made on clinical grounds and confirmed microscopically in 4, in 2 others it was suspected during life and in 1 it was discovered after death. Unfamiliarity with the disease may account for some of its assumed rarity. Familiarity with its general features reveals many cases that present a complex combination or succession of symptoms that sooner or later suggest the diagnosis.

## Indian Medical Gazette, Calcutta

**75**:513-576 (Sept.) 1940

Taking Blood for Transfusion (in Potain's Aspirator): Further Details Including Cold Storage. S. D. S. Greval, S. N. Chandra and A. B. Roy Chowdhury.—p. 513.
Buffer Precipitation Test for Malaria (B. P. T.) Adjusted for Large Scale Examinations. E. K. Wolff.—p. 517.
Observations on Differentiation of Bacterium Coli and Bacterium Aerogenes on Levine's Simplified Eosin Methylene Blue Agar as Applied to Bacteriology of Water in Bengal. S. Neogi.—p. 519.
Vibrio Cholerae and Other Vibrios: Observations on "Water Vibrios," with Special Reference to Their Variation During Storage in Culture Medium and Possible Relationship to Vibrio Cholerae. A. C. Vardon.—p. 522.
Modern Concept of Uremia and Its Clinical Study: Based on Series of 44 Cases. M. N. De and J. C. Banerjee.—p. 527.

## Journal of Laryngology and Otology, London

**55**:405-448 (Sept.) 1940

New Tests and Clinical Experiments on Hearing. F. W. Kobrak.—p. 405.

## South African Medical Journal, Cape Town

**14**:391-410 (Oct. 26) 1940

The Problem of Asthma. N. V. Storr.—p. 393.
Cholecystitis and Its Diagnosis. C. D. Brink.—p. 397.
New Operation for Inoperable Vesicovaginal Fistula. A. B. Taylor.—p. 401.

## Presse Médicale, Paris

**48**:689-704 (Sept. 4-7) 1940

*Bilateral Supradiaphragmatic Splanchnicectomy in Surgical Treatment of Arterial Hypertension. P. Wertheimer,—p. 689.
Modification of Induced Hyperglycemia by Ingestion of Fats. F. Sciclounoff and E. Martin.—p. 691.
Grave Paralysis in Course of Cerebrospinal Meningitis (Six Cases): Dangers Inherent in Intraspinal Injections of Sulfapyridine. P. Fort and M. Igert.—p. 693.
Value of Bromide Therapy, Single or Combined in Intravenous Administration. A. Landau.—p. 695.

**Supradiaphragmatic Splanchnicectomy in Arterial Hypertension.**—Wertheimer discusses bilateral splanchnicectomy by way of the posterior mediastinum based on 5 patients with arterial hypertension. Four of the 5 patients (aged 35, 43, 56 and 58 years, only one giving a familial history) had headache, vertigo, precordial pain and visual and nervous disorders associated with varying degrees of high blood pressure. The operation, which is described, succeeded in suppressing all subjective manifestations though it did not restore blood pressure to normal levels. Of 1 patient (aged 35 years) the arterial tension six months later was seen to be 175 mm. systolic and 125 mm. diastolic, though improved from the earlier 215 mm. systolic and 140 mm. diastolic gage; 2 others (1 aged 56) had subjective improvement which persisted though blood pressure levels were no lower. Splanchnicectomy, according to the author, is contraindicated for persons past 50, in renal lesions with significant urea retention and albuminuria and in cardiac involvements. Surgical intervention in persons older than 50 years needs to be supported by weighty considerations. Bilateral supradiaphragmatic splanchnicectomy, done in a single intervention, suppresses angiospastic states due to renal ischemia. It does not guarantee permanent vasodilatation in the splanchnic area but sets up a resistance to abnormal vasoconstriction. The author believes that the operation is not to be regarded as a therapeutic measure of last resort but one the applicability of which should be considered for patients past 50 who show a high diastolic pressure, a systolic pressure around 200, hypertensive retinitis, a somewhat enlarged cardiac shadow, a dilated heart responsive to digitalis and so on. He believes that a striking analogy exists between arterial hypertension with vascular neurotonia affecting the renal system and Raynaud's disease with vascular neurotonia disturbing the peripheral circulation.

**48**:721-736 (Sept. 17) 1940

*Possibility of a New Surgical Procedure for the Treatment of Definitive Facial Paralysis. R. Leriche.—p. 721.
Primary Tuberculous Infection and Exogenous Reinfection. E. Rist.—p. 722.

**Surgery for Facial Paralysis.**—Leriche proposes anastomosis between the sympathetic and the facial nerve for relief of facial paralysis. Twenty years ago his proposal to alleviate permanent lagophthalmos by section of the cervical sympathetic was favorably received and led to successful results at the hands of other surgeons. Admittedly a palliative operation, improvement was further sought by means of hypoglossal and spinal anastomosis, but without truly satisfactory results. Leriche now has come to believe that anastomosis can be combined with the section of the sympathetic in a simple operative procedure in which the sympathetic trunk is sutured end to end with the facial nerve. In this way the immediate advantages of sympathetic section could be combined with those of subsequent regeneration. Heterogenic regeneration thus envisaged finds support in the work of other investigators who found that the sympathetic can be neurotized by the vagus, the hypoglossal and nerves belonging to the spinal nervous system. The possibility that the sympathetic would admit of neurotization by nerves belonging to the cerebrospinal system was indicated by animal experiments of Ballance and his associates. Anastomosis of the central termination of the cervical sympathetic with the peripheral end of the facial nerve made possible the transmission of nerve impulses of cerebral origin to the periphery. Experiments on cats indicated that the sympathetic lent itself to neurotization by somatic nerves such as the facial. Ballance did not apply the results of these experiments to man. He propounded as the method of choice for facial paralysis fresh nerve grafting in the facial canal, which he found successful in experimentations on two monkeys. Leriche is of the opinion that anastomosis between sympathetic and facial nerve by virtue of its surgical simplicity offers a better surgical solution.

## Anales de Cirugía, Rosario

**6**:223-339 (Sept.) 1940. **Partial Index**

*Anthrax of the Kidney: Clinical Study. R. Ercole and A. Fort.—p. 263.
Treatment of Old Fractures of Neck of Femur by Subtrochanteric Osteotomy. O. R. Maróttoli.—p. 298.

**Anthrax of Kidney.**—Ercole and Fort call attention to the importance of pyelography in the diagnosis of renal anthrax. They report 4 cases in which the preoperative diagnosis was made by pyelography. Renal anthrax is more frequent than is believed. It frequently causes perirenal abscess and may pass unobserved unless pyelography is systematically practiced in the presence of such an abscess. The patients give a history of suppuration in regions remote from the kidney, such as furuncles and felons, one or two months before the appearance of renal symptoms. Pain in the lumbar region and symptoms of general infection predominate over those of the perirenal abscess in some of the cases. The urine does not contain pus cells. The diagnosis is arrived at by pyelography, which reveals the tumor or abnormalities in the renal pelvis and renal calices or displacement of the structures by compression. The treatment consists in either partial or complete nephrectomy or enucleation of the tumor. Nephrectomy is indicated when the tumor occupies a considerable portion of the renal parenchyma or is situated centrally. In the cases reported by the authors the preoperative diagnosis was confirmed by macroscopic and microscopic studies of the kidney removed by nephrectomy. Recovery took place in all cases.

## Clinica Ostetrica e Ginecologica, Rome

**42**:473-520 (Oct.) 1940. **Partial Index**

*Diagnosis of Rupture of Amnion. A. La Delfa.—p. 473.
Malignant Granuloma in Pregnancy. A. de Palo.—p. 477.

**Diagnosis of Rupture of Amnion.**—According to La Delfa there are cases of dystocia in which cesarean section is indicated and in which diagnosis of rupture of the bag of waters is necessary and difficult. Results of tests based on variations of the $p_H$ of the vaginal secretion are not reliable. La Delfa investigated the diagnostic value of von Numers' test (See *Acta obstetricia et gynecologica Scandinavica* **16**:249, 1936). The test is based on the occurrence in the vaginal secretion of free drops of fat or cells of fetal sebaceous glands derived from vernix caseosa. A drop of vaginal secretion is taken from the vagina with a platinum loop and is spread on a slide carefully defatted. The slide is air dried without previous fixation, stained at room temperature in a solution of 0.2 or 0.3 Gm. of sudan III in 100 cc. of 70 per cent alcohol, washed in water, dried with blotting paper and immediately examined with low magnifying power. Fetal fat substances are stained a distinct orange red. They must be differentiated from particles of mucus and fat droplets of vaginal epithelial cells, which stain a faint yellowish pink. Abundance of fat particles in the vaginal secretion justifies the presumption that rupture of the membranes has taken place. Negative sudan reaction speaks for the reverse. In a series of 160 cases reported by the author, the test was negative in a group of 50 pregnant women at full term and in a group of 62 women at labor with intact bag of waters. The test was positive in a group of 35 women in labor shortly after the rupture of the membranes and during the first twenty-four hours after the rupture and in 12 of 13 women twenty-four or forty-eight hours after the rupture. When positive, the test is an absolute proof of rupture of the membranes.

## Deutsche medizinische Wochenschrift, Leipzig

**66**:337-364 (March 29) 1940. **Partial Index**

Prophylactic Treatment of Gas Edema After Gunshot Injuries. N. Guleke.—p. 337.
*Present Status of Control of Anaerobic Wound Infections. J. Zeissler.—p. 340.
Surgical Experiences in the Polish War. H. Wildegans.—p. 343.
Amputation of Limbs. H. Bürkle-de la Camp.—p. 347.
Value of Tomography for Localization of Foreign Bodies. W. Kremer.—p. 351.
Gas Gangrene. M. Westenhöfer.—p. 353.
Results of German War Surgery in Past Centuries. W. von Brunn.—p. 353.

**Anaerobic Wound Infections.**—According to Zeissler the most feared wound infections during war are tetanus, gas gangrene and malignant edema. Gas edema is a collective term for gas gangrene and malignant edema, which frequently

develop as mixed infections. The majority of gas edemas, particularly gas gangrene, are produced by Clostridium welchii (B. perfringens). The next most frequent gas edema organism is Novy's bacillus of malignant edema (B. oedematiens) and still another is the Vibrion septique. These bacilli were known before 1895. Since that time the following gas edema bacilli have been discovered during and after the World War: Bacillus histolyticus, Bacillus oedematicus sporogenes, Bacillus haemolyticus, Bacillus gigas and three organisms that are only toxicologically differentiable from Bacillus welchii, namely Bacillus agni, Bacillus ovitoxicus and Bacillus paludis. The latter three have never been observed in human subjects. The rauschbrand bacillus (B. chauvaei) was discovered in 1881. The knowledge regarding gas edema is far in advance over what was known at the beginning of the World War. Not only are the organisms known which cause it, but also the frequency of their occurrence in the soil of different battle fields. Gas edema serum is a valuable adjuvant to the surgical treatment of gas edema. The fact that the time elapsing between the injury and the outbreak of the gas edema is usually short makes quick action important. This action consists in a thorough surgical cleansing of the wound which removes all foreign bodies, dirt and necrotic and nonviable tissues and, if necessary, of administering specific antitoxins in the form of serum. In view of the short incubation period and the rapid course of gas edema, small doses of serum are inadequate for prophylaxis as well as for treatment. Recent investigators, among them Löhr and Konjetzny, administer from 300 to 500 cc. of gas edema serum, chiefly by means of the intravenous drip. The gas edema serum contains antitoxins against the most important gas edema bacilli: (1) Bacillus welchii, (2) Novy's bacillus of malignant edema (B. oedematiens), (3) Vibrion septique, (4) Bacillus histolyticus. In view of the fact that large quantities of gas edema serum are required for effective action, its administration should be limited to the cases in which either gas edema has already developed or in which the severity of the wound or the local frequency of gas edema make serotherapy advisable. The author maintains that local chemotherapy is ineffective and warns against the injection of chemicals in the surroundings of the wound. Such injections may cause trophic disturbances in the tissues or even tissue necroses and thus provide one of the factors favoring the development of gas edema.

**66**:393-420 (April 12) 1940. **Partial Index**

Metabolic Experiments on Protein Supply of German People During Winter of 1939 to 1940. A. Bickel.—p. 393.
*Prophylaxis of Scarlet Fever. W. Schultz.—p. 396.
*Control of Fatigue by Autogenous Active Substances. T. Morell.—p. 398.
Chemotherapy for Reduction of Treatment Time in New Gonorrhea. Lindemann, Felke and Schleiff.—p. 401.
Origin and Development of Nonpigmented Forms of Malaria Parasites. W. Schulemann and K. Spies.—p. 404.
Utilization of Mushrooms. E. Nossell.—p. 405.
Studies on Chemotherapy of Tuberculosis. E. Hesse and Gertrud Meissner.—p. 407.

**Prophylaxis of Scarlet Fever.**—Schultz places especial emphasis on a sufficiently prolonged isolation in the prophylaxis of scarlet fever. The biologic prophylaxis is accomplished at his clinic chiefly with human serum. The efficacy of horse immune serum is established, but its extensive application for prophylactic purposes is inadvisable because, in addition to possible immediate complications, there is danger that later administration of horse serum (tetanus antitoxin and so on) may provoke severe reactions. It is likewise probable that the protective action of the serum rapidly diminishes. In view of these disadvantages of horse serum in the prophylaxis of scarlet fever, passive immunization with convalescent serum has been recommended. This serum is obtained between the fourth and the sixth week of the disease. Because collection of convalescent serum involves difficulties, attempts have been made to utilize serum of adults. It has been proved by Wiecke and others that, with increasing age, persons become more and more immune to scarlet fever, even though they have not had the disease, and that the serum of adults of comparatively advanced age (40 and up) is more effective than the convalescent serum. The author is unable to explain this immunobiologic phenomenon but accepts it as a fact, the more so since normal human serum is also of therapeutic value. In a number of cases in which scarlet fever was anticipated, the author administered 10 or 20 cc. of serum from adults with the result that scarlet fever did not develop. He admits, however, that this is not a definite proof of the prophylactic value of the serum. The active method of immunization has been used less extensively. It employs a scarlet fever vaccine which, in addition to killed scarlet fever streptococci, contains an anatoxin. This vaccine, however, may cause a general reaction in sensitive persons. Combination of passive and active immunization is also possible. The use of serum from adults makes the problem of biologic prophylaxis of scarlet fever much less complicated than it was formerly. The serum is obtained from patients who have hypertension, polycythemia and other conditions and who are free from infectious disease. Serum is stored in an icebox. Observation of necessary precautions obviates harmful effects.

**Control of Fatigue by Active Substances.**—The problem of fatigue demands particular attention at the present time, according to Morell. Fatigue reduces performance. The problem becomes urgent in aviators who have to fly at high altitudes where they have to resort to oxygen respiration. The cold and prolonged exposure to the noise of the motor increase the fatigue beyond physiologic endurance. The reaction capacity becomes greatly decreased. Means for removal and detoxication of fatigue substances are therefore much to be desired. If the performance capacity is to be increased, it is advisable to supply the organism by way of food with sufficient biocatalytic agents and with energy producing substances. Not only must they be supplied in adequate quantities, but physiologic proportioning is important. The author mentions vitamin C and B complex as important activators and dextrose as an important foodstuff molecule. The proper caloric utilization of dextrose is possible only in the presence of physiologically adequate amounts of vitamins B and C. The author reviews the mode of action of these vitamins and describes work test experiments in the course of which he studied the effect of a preparation containing dextrose and vitamins B and C. He found that performance increases greatly if the preparation is given during extreme fatigue. He recommends its use in the course of exertion.

**66**:729-756 (July 5) 1940. **Partial Index**

Treatment of Open Fracture of Cranial Vault. F. Heck.—p. 731.
Treatment of Febrile Mastitis During Puerperium with Special Consideration of Use of Short Waves. H. Jacobi.—p. 734.
Therapeutic Use of Thionine in Dextrose in Anoxia: Foundations of This Therapy. W. Herbrand and K.-H. Jaeger.—p. 736.
*Intrasternal Injection and Transfusion as Substitute for Intravenous Methods. N. Henning.—p. 737.
Treatment of Dermatoses During War. Mohrmann.—p. 739.

**Intrasternal Injection and Transfusion.**—Henning found in a number of experiments that substances injected into the spongiosa or medullary cavity of the sternum find their way quickly into the blood stream by way of the internal mammary vein. He investigated the question of substituting intrasternal injection or transfusion for intravenous injection or transfusion. He found that sternal injections of strophanthin, of hypertonic solutions of sugar or of sodium chloride and of other intravenously administered medicaments are tolerated without reactions and that it is possible to give blood transfusions in this manner. After puncture, an irrigator containing blood is attached and the blood is allowed to run in from an elevation of 1 meter. The inflow velocity is slightly less than in the case of intravenous transfusion. The inflow may be made faster by attaching two needles to the tube. Sternal injection or transfusion is indicated in cases in which it is difficult to find veins in the extremities, or in vascular collapse which no longer permits adequate filling of the veins. It should be valuable under war conditions, when an intravenous injection or a blood transfusion becomes necessary during collapse, after severe injuries or great loss of blood. The sternal transfusion has the advantage that the cannula requires no particular attention, because it stands fixed in the compact mass. The technic of sternal puncture is so simple that it involves no difficulties. The author makes the puncture in the midline of the third, fourth or fifth intercostal space. He uses local anesthesia for the skin, subcutis and periosteum and, since the periosteum is extremely sensitive, he places several small subperiosteal depots of procaine hydro-

chloride. After the needle has reached the external compacta, several turning movements are made to penetrate it. The instrument is fixed with the left hand in order to prevent a sudden deep penetration.

### 66:785-812 (July 19) 1940. Partial Index

*Present Status of Knowledge on Etiology and Epidemiology of Hodgkin's Lymphogranulomatosis. P. Uhlenhuth and K. Wurm.—p. 785.
Therapeutic Results in Brain Tumors by Roentgen Irradiations of Closed Cranium. Lucie Rüsken-Brosowski.—p. 790.
Paralyzing Effect of Opiates on Respiratory Function. F. Eichholtz.—p. 792.
Possibility of Selective Heating of Some Tissue Layers in Ultra-Short Wave Condenser Field. E. Hasché.—p. 797.
Periproctitic Abscesses and Anal Fistulas. P. Rostock.—p. 800.

**Etiology of Hodgkin's Lymphogranulomatosis.**—Uhlenhuth and Wurm review the present status of the etiology and epidemiology of Hodgkin's lymphogranulomatosis. They submit the results of studies carried on over a period of several years in collaboration with clinics as well as reports from the literature. They had investigated the question of Hodgkin's disease being infectious. This theory has found wide acceptance because of the clinical course, the anatomic character of the lesions and certain epidemiologic aspects. Various types of micro-organisms have been demonstrated in the excretions, the blood, the glands and the organs of patients with Hodgkin's disease and have been suggested as causal organisms. The most stubbornly defended theory was that of tuberculous etiology, first suggested by Sternberg in 1898. This problem was studied in 70 cases. The bacterioscopic demonstration of tubercle bacilli with the Ziehl-Neelsen method and with methods to bring about abundant growth of the organism has invariably failed. The guinea pig test was positive in 3 of 33 cases. In 1 of the 3 cases necropsy revealed that active generalized tuberculosis coexisted with Hodgkin's disease. Because of L'Esperance's claim that the typus gallinaceus of the tubercle bacillus is the causal agent they inoculated chickens with material from patients with Hodgkin's disease, but none of the chickens contracted tuberculosis. They admit that many problems of the relationship between Hodgkin's disease and tuberculosis require further clarification, but on the basis of the available evidence the etiology of Hodgkin's disease has no relation to tuberculosis because (1) the demonstration of tubercle bacilli in Hodgkin's disease is not frequent enough, (2) Hodgkin's disease differs immunobiologically from all forms of tuberculosis, (3) roentgenotherapy is well tolerated in Hodgkin's disease and poorly in tuberculosis, (4) there is no form of tuberculosis which is as fatal as Hodgkin's disease, (5) the local differentiation of the lesions in case of existence of the two contraindicates identical etiology, (6) if Hodgkin's disease had a tuberculous etiology it should be possible to produce it in the animal experiment. In connection with the virus theory the authors direct attention to Gordon's test, which while diagnostically valuable, is not specific. The virus theory has not been demonstrated. Although an increasing number of investigators classify Hodgkin's disease with neoplastic diseases, sufficient proof for it does not exist. According to some statistics the deaths from Hodgkin's disease amount to about 120 per 10,000,000 people annually. The geographic distribution varies. In some countries an increase has been observed in recent years. The authors doubt the higher incidence in the age group between 20 and 40 but cite a large statistical material from the United States, which indicates that the disease increases with age. The same material also proves the higher incidence in men than in women (100 men to 57 women).

### 66:813-840 (July 26) 1940. Partial Index

Experimental Foundation of Headache Therapy. G. Schimert Jr.—p. 813.
*Glossopharyngeal and Trigeminal Neuralgia and Its Treatment with Snake Venom. W. Behrmann.—p. 817.
Physical Therapy in After-Treatment of War Injured. H. Adam.—p. 819.
Balneotherapy of Members with Impaired Movement and of Poorly Healing Wounds. K. Schnelle.—p. 821.
Otogenic Brain Abscess and Its Treatment. A. Herrmann.—p. 824.
Is Bechterew's Disease a Spondylarthritis? E. Guntz.—p. 826.
Azosulfamide in Therapy of Anthrax. J. Dörffel.—p. 827.

**Snake Venom in Neuralgia.**—Behrmann knows of no systematic investigations on the use of snake venom in the treatment of neuralgias in the region of the face and head. He reports 3 cases of his own in which he resorted to this treatment. The first patient, a woman aged 54, for five months had suffered from severe pains in the tongue. Lightning-like extreme pains were felt first after eating and later when opening the mouth or speaking. Several weeks later, peculiar taste sensations were experienced. The swallowing of dry foods became painful and later impossible. Treatment with various analgesics and with nonspecific vaccine therapy was ineffective. Snake venom in the amount of 0.25 cc. was injected deep into the muscle. This was increased after an interval of three days to 0.5, and later to 1 cc. Injections of 1 cc. of the venom were administered once or twice weekly. After three weeks of treatment the patient was entirely free from pain and her general appearance was greatly improved. She gained in weight and has remained free from pain for over a year. The second patient had trigeminal neuralgia. Ten injections of snake venom produced complete freedom from pain. In the third patient with trigeminal neuralgia the effect of venom therapy was not so favorable. This woman, however, had leontiasis ossea, and the anatomic changes in the cranial bones were responsible for the neuralgia. In the other two there existed general and cerebral arteriosclerosis. Arteriosclerotic neuritis is especially likely to develop in the trigeminal nerve because its root area has few vessels and is exposed to pontile circulatory disturbances. Snake venom in addition to the analgesic effect possesses cytolytic and proteolytic effects on the vascular endothelium. It reduces blood pressure, produces a more favorable circulatory state, increases the metabolism of the nerves and counteracts the neuralgic pain.

## Geburtshilfe und Frauenheilkunde, Leipzig

### 2:387-440 (Aug.) 1940

Question of Correctness of Concept of Primacy of Ovum. L. Seitz.—p. 387.
*Prognosis and Possibilities of Modern Therapy of Febrile Abortion. W. Benthin.—p. 393.
Therapy of Early Puerperal Mastitis: Local Application of Synthetic Estrogenic Substances. E. Leinzinger and R. Bayer.—p. 414.
Inversion of Uterus Developing in Connection with Labor or as Sequel of Tumors. A. Ebergényi.—p. 425.
Late Results of Therapy of Amenorrhea by Means of Intraovarian Injections of Hormone Preparations. C. Stanca.—p. 433.

### 2:441-494 (Sept.) 1940. Partial Index

*Prognosis and Possibilities of Modern Therapy of Febrile Abortion. W. Benthin.—p. 444.
Fat Tissue Flaps from Bulbocavernous Region as Protective Plastic Operation in Sutures of Fistulas. H. Martius.—p. 453.
Relapse in Endometriosis. F. Movers.—p. 460.
Giant Ovarian Cysts. L. Lajos.—p. 475.

**Prognosis and Therapy of Febrile Abortion.**—According to Benthin, complications are to be anticipated in approximately 15 per cent of febrile abortions. The mortality rate is 7 per cent, much higher than in febrile puerperal states. Of patients with para-uterine infections at the time of hospitalization, 31 per cent die. A considerable number remain sterile and those with primary recovery may develop later sequels. Expectant treatment offers best results in cases in which infection is confined to the uterus. Spontaneous expulsion takes place under expectant treatment in from one sixth to one third of the cases. Quinine and ergotamine tartrate promote the expulsive efforts, especially if employed with vaginal tamponade. This tamponade stimulates uterine contractions and prevents excessive loss of blood. The use of carbon and of the ice bag are valuable in restricting the infectious process to the uterine cavity. Early medication with sulfanilamide is advisable for the prevention and arrest of general septic infections and in peritonitis. The expectant treatment requires strict bed rest. A well planned expectant treatment prevents sepsis and pyemia and para-uterine infections. The operative evacuation of the uterus can be tried without much danger five days after the fever has subsided. An earlier or immediate surgical evacuation is permissible only in extremely urgent cases. There exists no vital indication for operative evacuation as long as the cervical canal is still closed. This should be kept in mind especially in the presence of parametritis, peritonitis and inflammations of the adnexa. If the cervical canal is open and if severe hemorrhage exists, interventions are permissible and, if placental parts are already undergoing expulsion, their removal is indicated.

The digital method is the most reliable and least harmful. It should be performed in deep anesthesia and as carefully as possible. Introduction of carbon into the evacuated uterus promotes detoxication and rapid discharge of secretions. Azosulfamide, dextrose, continuous infusions, administration of vitamins and blood transfusion are the most important aids in the treatment of infection. All febrile abortions should be treated in a hospital.

## Medizinische Klinik, Berlin

**36**:699-730 (June 28) 1940. **Partial Index**

Protection of Those in Danger of Psychopathic Development. J. H. Schultz.—p. 699.
Prophylactic Surgical Wound Therapy at the Front. G. Schöne.—p. 703.
Prophylaxis and Treatment of War Epidemics (Dysentery, Typhoid, Influenza). H. Löhr.—p. 705.
*Nonsurgical Treatment of Thyrotoxicoses. H. Wiebel.—p. 707.
*Symptomatology of Coronary Thrombosis. R. Bürklen.—p. 709.
Pathogenesis of Tetanus. H. zur Horst Meyer.—p. 711.
Prevention of Dental Caries. H. Goll.—p. 712.

**Nonsurgical Treatment of Thyrotoxicosis.**—According to Wiebel, thyrotoxicosis is mainly a disease of women (3:1) particularly common during the years when family and occupation make the greatest demands. Although disturbances in the correlation between the sympathetic nervous system and secretory glands play an important part in the pathogenesis of the disease, the problems of life and environment undoubtedly contribute much. One of the most important features of the internal treatment is to change these conditions by hospitalizing the patient. Internal treatment including roentgen therapy, should be tried in the mild and in some moderately severe cases of thyrotoxicosis. Therapy with phosphorus and arsenic preparations, various diets, iodine, fluorine, vitamin A, injection of animal blood and roentgen rays is reviewed. Observations made in over 400 cases treated at the author's clinic in the course of the last two years indicate that no internal treatment offers permanent results in the severe and in most of the moderately severe cases of thyrotoxicosis. The author regards surgical treatment as the method of choice in all severe and moderately severe cases of thyrotoxicosis.

**Symptomatology of Coronary Thrombosis.**—Bürklen describes a new symptom which he thinks may be of value to the general practitioner. He has demonstrated that in patients with coronary thrombosis with subsequent myomalacia cordis the temperature may differ in the two axillas. This difference, which may amount to as much as 1.2 degrees C. (2.16 degrees F.), is due to the vasoconstrictive irritation originating in the diseased portion of the coronary artery. The temperature is lower in the axilla of the diseased side. Thus, if a branch of the left coronary artery is obstructed, the temperature will be lower in the left axilla. This behavior of the axillary temperature results only from coronary occlusion. The symptom is of differential diagnostic value in thoracic diseases, particularly in pneumonia and in pleurisy, two disorders which are especially difficult to differentiate from coronary thrombosis.

**36**:763-794 (July 12) 1940. **Partial Index**

Care of the Eyes of Soldiers in the Field. W. Gilbert.—p. 763.
What Can Be Expected from Protective Inoculation Against Typhoid and What Preparations and Methods Are to Be Recommended? M. Gundel.—p. 764.
Achylic Nervous Disorders. K. W. Essen.—p. 766.
*Teschen Paralysis of Hogs and Possible Relationship to Disorders of Central Nervous System in Human Subjects: Importance of Cooperation Between Physician and Veterinary. A. Kment.—p. 769.
Infectious Chorea Minor: Diagnosis, Cause and Treatment. H. Stefan.—p. 770.
Treatment of Epidemic Meningitis. E. Türk.—p. 774.
Regulation of Evacuation of Bowels. W. Kaufmann.—p. 775.

**Paralysis of Hogs and Central Nervous System Disorders in Man.**—According to Kment, since 1929 an infectious paralysis has been observed among hogs which is referred to as Teschen paralysis, because it appeared first in a locality named Teschen. The causative agent is an ultravisible, filtrable, neurotropic virus. The disease has been named "encephalomyelitis non purulenta enzootica suum." The paralysis affects particularly the posterior extremities but may involve the anterior ones as well. If the animals do not die of respiratory paralysis early in the disease, the disorder may persist for months. The animals usually have fever. The symptomatology and the microscopic appearances of the central nervous system recall human poliomyelitis. The author admits, however, that similarity in the microscopic picture does not establish identity of the disease. It has not so far been transmitted to human beings, and injections into monkeys were not successful. Many problems connected with this hog paralysis are still unsolved, but the author suggests that Frauchiger's observations on poliomyelitis in a heifer and in hogs (see THE JOURNAL, July 2, 1938, p. 74 and *Schweiz. med. Wchnschr.* **69**:71 [Jan. 28] 1939; abstr. THE JOURNAL, March 25, 1939, p. 1202) are of interest in this connection. He thinks that the disease which Frauchiger observed was Teschen paralysis, a disease which until then had never been observed in Switzerland. A connection may exist between this paralysis in hogs and the "maladie des jeunes porches" (disease of young swineherds) which has been observed in the Swiss-French border region (see *Schweiz. med. Wchnschr.* **67**:709 [July 31] 1937; abstr. THE JOURNAL, Sept. 25, 1937, p. 1083) and which is a form of serous meningitis, possibly an abortive form of poliomyelitis. There is no proof of identity of the Teschen paralysis of hogs and of poliomyelitis, although the similarity of the symptoms of the two diseases is striking.

## Münchener medizinische Wochenschrift, Munich

**87**:877-904 (Aug. 16) 1940. **Partial Index**

*Chief Problems of Bright's Disease. F. Volhard.—p. 877.
Surprising Blood Picture in Old People. K. Bürker.—p. 882.
Sex, Age and Occupational Distribution in Ventricular and Duodenal Ulcer. A. Weidinger.—p. 882.
Prevention and Treatment of Soreness of Nipples During Nursing Period. A. Poerschke.—p. 885.
Experiences with Calcium-Bromine Therapy in Dermatology and Venerology. O. Schuester.—p. 886.
Economics in Staining of Gonococci and Spirochetes. H. Lipp.—p. 888.

**Bright's Disease.**—According to Volhard the problems presented by Bright's disease concern chiefly its pathogenesis. He poses the question of the bilateral hematogenic or internal renal disease as contrasted with the urologic or surgical diseases of the kidney, as involving practically the entire organism: the brain, eye, skin, circulation, heart, arteries, blood and lymph capillaries, blood, bone marrow, water exchange, acid-base equilibrium and the metabolism. Three factors are of importance in this connection: (1) the decrease in the secretory activity of the kidney, (2) the increase in the permeability of the renal membranes, particularly of the glomeruli, and (3) the disturbed blood perfusion of the glomeruli. Until recently nearly all remote symptoms of kidney disease were ascribed to failure of its secretory function. The introduction of the water and concentration tests has made it possible to investigate which of the numerous remote effects occur with and which occur without the disturbance of the renal function. It was found that the most striking symptoms, such as dropsy, hypertension, albuminuric retinitis and convulsive uremia, occur also in the absence of renal insufficiency. This raised the question as to the part renal insufficiency plays in the disease. Renal insufficiency is due to a decrease in the number of secretory elements manifested in the qualitative change in the secretory function which begins with a reduction in the concentration capacity and compensatory polyuria, which passes into isosthenuria and pseudonormaluria; that is, secretion of a blood isotonic urine of the specific gravity of deproteinized blood in reduced quantities. If in the presence of isosthenuria the quantity of urine sinks below 1 liter, the condition is irrevocable. The clinical picture of absolute renal insufficiency, true uremia, is that of intoxication. There is a shifting of the acid-base balance toward the acid side; there are inflammatory changes in the skin, pericardium, larynx, pharynx, stomach and intestine. Toxic irritation of the nervous system is indicated by involuntary muscle spasms and subsultus tendinum. There is a toxic impairment of erythropoiesis. The development of renal insufficiency and true uremia may be so insidious that the physician does not think of renal disease but of pulmonary or cardiac disorder. However, increased respiration the result of acidosis differs from that of cardiac or pulmonary dyspnea. There is present the characteristic lack of color of the urine, a specific gravity of about 1.010 and xanthoproteic test of Becher. It is also necessary to recognize cases

of relative renal insufficiency that are compensated by polyuria. These cases are characterized by dyspeptic manifestations, lack of appetite, aversion to meat and unquenchable thirst. The second important factor in Bright's disease, namely the increased permeability of the renal membranes, particularly of the glomeruli for albumin, becomes serious only if the loss of albumin in the urine exceeds the capacity of the liver to form blood protein. This process, which results in hypoalbuminemia, is often favored by the prescription of an unsuitable, protein deficient diet and is followed by hunger edema. In these cases of protein hunger the dropsy is of extrarenal origin; its development during nephrosis has no connection with a decrease in the renal secretion but is caused by the increased permeability of the kidney. The third factor, the disturbance of the renal or glomerular blood perfusion, is the most important since it causes most of the remote symptoms. Cardiac hypertrophy of Bright's disease develops on the basis of increased blood pressure. The disturbance in renal blood perfusion activates the chemical hematogenic mechanism, which produces pale hypertension in the form of a generalized vascular contraction, which at its height gives the impression of a general arterial ischemia. The latter is at the basis of some of the clinical symptoms which formerly were regarded as toxic or uremic, namely albuminuric retinitis, convulsive uremia, pseudo-uremia, symptoms of cerebral pressure with headache, vomiting, choked disk, amaurosis and fatigue, as well as cardiac symptoms in the form of asthma or of angiospastic coronary insufficiency. Kidney diseases in which blood perfusion is not impaired have a much better prognosis.

## Wiener klinische Wochenschrift, Vienna

**53**:637-656 (Aug. 9) 1940

*Diagnosis and Treatment in Swelling of Brain. M. de Crinis.—p. 637.
Treatment of Epidemic Meningitis with Azosulfamide. W. Maier.—p. 640.
*Bence Jones Albuminuria. E. Dworacek.—p. 641.
Therapeutic Experiments with Organ Specific Lipoid Extracts. A. Ringl.—p. 644.

**Swelling of Brain.**—According to de Crinis it is necessary to differentiate between swelling and edema of the brain. Swelling of the brain is an enlargement in volume which is not a direct result of hyperemia, cerebral edema or hydrocephalus. The chief difference between swelling and edema is that in swelling the water content of the brain is less and the consistency is greater than in edema. The increased volume in swelling of the brain infringes on the available space and choked disk, signs of vagal irritation (slow pulse and nausea) and headaches appear. For the necroscopic diagnosis of brain swelling it is essential that the necropsy be made shortly after death, for, if considerable time elapses, brain swelling may result from the postmortem absorption of cerebrospinal fluid. The macroscopically visible signs of brain swelling are flattening of the convolutions and reduction of the cerebrospinal fluid spaces and of the subarachnoidal space; also the consistency of the brain is increased and it is comparatively dry and sticky. Brain swelling is regularly found following death during status epilepticus, status paralyticus, uremia, puerperal eclampsia, after sudden death in catatonic excitation, from electrical brain lesions and from inflammatory diseases of the brain such as encephalitis and meningitis, and from cerebral abscess. In children who died suddenly, brain swelling has been known to be the only pathologic manifestation. The author gives particular attention to brain swelling in cerebral tumors. The swelling of the brain does not parallel the size of the brain tumor. Fist-sized tumors on the frontal brain may exhibit no signs of spatial limitation, whereas small tumors, the size of a cherry, may produce pressure and sudden death. Brain swelling with the acute signs of cerebral pressure often develop after transportation of patients with cerebral trauma or tumor. Incidence and extent of brain swelling are determined by the type of tumor. Tumors with infiltrating growth such as gliomas cause swelling more readily than circumscribed tumors. Meningiomas cause brain swelling only after they have reached a certain size. Swelling of the brain is rare in the presence of angiomas. The clinical symptoms of brain swelling may be fleeting at first and they may not be limited to the immediate vicinity of the focus of the disease but may involve distant regions. The fleeting character and the mildness reveal that they are neighborhood or distant symptoms rather than focal or nuclear symptoms. Response to treatment may likewise be of help in determining whether symptoms are caused by brain pressure or by a tumor. The author discusses measures effecting dehydration which not only reduce the pressure on the brain but also permit a conclusion regarding the cause of the swelling. Urea plays an important part in tissue metabolism and in the physicochemical condition of the tissues. The author was able to demonstrate urea in the brain tissue of patients in whom cerebral tumor or abscess, encephalitis, status epilepticus or delirium tremens had produced brain swelling. He is convinced that swelling of the brain is chiefly a physicochemical problem. The living brain contains lipoids and protein bodies which are in different states of swelling. The state of swelling is dependent on humoral, toxic and other influences. In swelling of the brain, the tendency of the colloids to absorb water is increased beyond physiologic limits. In edema of the brain the absorption tendency is reduced and water is given off. This differing physicochemical behavior of the brain colloids is due to pathologic processes some of which are still unknown.

**Bence Jones Albuminuria.**—Many investigations have been made to determine the characteristics and the origin of the Bence Jones protein of the urine of patients with multiple myeloma and of some with chronic leukemia. These studies, according to Dworacek, and those on the blood protein bodies of patients with Bence Jones albuminuria have not produced uniform results. The investigators are divided on the question whether the Bence Jones protein is of exogenic or of endogenic origin. On the basis of the extensive investigations of Magnus-Levy it is now generally assumed that the elimination of Bence Jones protein is largely dependent on the nitrogen metabolism. It is not a purely autogenous product but is influenced by various food proteins. The author reports studies on a patient with multiple myeloma. The protein was isolated from the mixed urine during a time when the patient was on a diet with a relatively restricted protein intake. The method used was that of Mainzer. It was found that the average daily elimination of Bence Jones protein was 2 Gm. The protein solution as well as the urine produced the customary precipitation expected of a Bence Jones protein body: (1) beginning flocculation at 60 C., maximal turbidity at 65 C., clearing at 80 C., complete clarification at 97 C. and precipitation on renewed cooling; (2) flocculated precipitation on addition of a 25 per cent solution of nitric acid, heat solubility; (3) precipitation with 12.5 per cent solution of hydrochloric acid and liquefaction in heat; (4) precipitation with ferricyanic acid and redissolving on heating; (5) irreversible precipitation on addition of 96 per cent alcohol and other precipitation reactions. An analysis of the purified dry substance of the isolated protein revealed that the values determined differed from those obtained by others. The author thinks that this is due to the fact that the Bence Jones protein is not a definite chemical entity but that its composition is determined by physiologic conditions and particularly by the nitrogen metabolism. Six months later, when the patient still received the same diet, the tests were repeated and practically the same results were obtained. The patient was put on a meat diet with a high protein content and after two weeks the urine was collected and Bence Jones protein was isolated again. A comparison of the values found on analysis of the Bence Jones protein obtained in the three successive examinations disclosed during the third an increase in nitrogen, tryptophan, arginine and particularly tyrosine, whereas sulfur, cystine and hystidine had remained practically the same. These results make probable a dependence of the Bence Jones protein on food proteins. The author did not succeed in isolating the Bence Jones protein from the blood, but he points out that the sedimentation speed of the erythrocytes is increased in patients with multiple myeloma. Since the Bence Jones protein has the colloid character of serum albumin, he decided to investigate the dependence of the sedimentation reaction on this protein. He made the surprising discovery that the addition of a solution of Bence Jones protein to normal blood considerably retards the sedimentation speed and he thinks that the albumin character of the Bence Jones protein is responsible for this.

**53**:697-716 (Aug. 30) 1940

*Single Massive Doses in the Therapy and Prevention of Rickets. G. O. Harnapp.—p. 698.
Contraselection. K. Keller.—p. 701.
The Health Wagon (Motorized Preventive Medicine for Rural Districts). F. Hamburger.—p. 703.
Origin and Value of the Health Wagon. Adele Bornefeld.—p. 704.
Experiences with First Health Wagon in Zwettl District, Lower Danube. H. Goll.—p. 705.

**Vitamins $D_2$ and $D_3$ in Rickets.**—Harnapp found single massive doses of from 10 to 15 mg. of vitamin $D_2$, orally administered, of sufficient concentration to effect the cure and prevention of rickets. He claims for this dosage the regeneration of even pronounced rachitic osteomalacia. Prolonged tests were made on some 100 clinically controlled inmates of a children's home. Analyses of feces showed that 93 per cent of the vitamin was retained in the body. Craniotabes generally diminished after four to five days and often ceased to be palpable from eight to ten days after the single treament. Blood chemistry assays indicated respectively mounting phosphate or calcium levels after fourteen to twenty-four hours. Spontaneous fractures rapidly developed callus formations. Calcic regenerative processes were roentgenologically seen to occur after four days. Vitamin $D_2$ was likewise therapeutically significant in spasmophilia and in complications with pertussis and pneumonia. Its prompt effect in general well-being was surprising. Querulous and apathetic children of preschool age suffering from severe rickets were observed several days after the vitamin was given to indulge in play and hilarity. Roentgen, blood and electrocardiographic tests failed to disclose any toxic effects of massive dosage. Experiments with vitamin $D_2$ in the prevention of rickets, carefully controlled for a sufficiently long period of time on a large number of children, indicated that 7.5 mg. was the minimum safe dose. Experiments with vitamin $D_3$, on the other hand, seemed to show a slight superiority of this vitamin over vitamin $D_2$, since 5 mg. of $D_3$ achieved the same prophylaxis as 7.5 mg. of $D_2$. However, further investigations of the relative potency of $D_2$ and $D_3$ are in order. In view of the difficulty of determining the initial onset of rickets after the first six months of neonatal life, the author is of the opinion that all nurslings and infants, irrespective of their physical appearance, should be prophylactically treated with vitamin $D_2$ in the dosage indicated. He thinks that rickets could be completely abolished if this preventive measure was universally applied. To insure the child's welfare against the well known therapeutic laxness of the public when visible signs of the disease are absent, medication should be done by the physician himself.

## Zeitschrift für Urologie, Leipzig

**34**:249-304 (No. 6) 1940. **Partial Index**

*Experiences and Results with Endo-Urethral Resection of Prostate. A. Röbbelen.—p. 249.
Foundations of Pathologic Pyelogram. A. Herzog.—p. 273.
Early Roentgenologic Diagnosis of Renal Tuberculosis. O. Olsson.—p. 283.
Temporary Subcapsular Hemostasis in Nephrotomy in Situ. B. von Mezö.—p. 294.

**Endo-Urethral Resection of Prostate.**—Röbbelen points out that the enthusiasm for the endo-urethral resection of the prostate, which in some clinics led to its application in 99 per cent of the cases of hypertrophy of the prostate, has somewhat diminished in the last few years, because complications and failures were observed. Hemorrhage, rupture of the bladder, inflammation of the pelvic floor and peritonitis as immediate sequels, and infections, incontinence and rectovesical fistulas as late complications were reported. Endo-urethral interventions are often followed by a prostatitis, cystitis and great irritability of the bladder more annoying than the difficulties in micturition. A number of surgeons, however, hold a favorable opinion of the endo-urethral resection. The author discusses the indications and the results with endo-urethral electroresection for hypertrophy of the prostate on the basis of 100 electroresections and forty-one follow-up examinations in Konjetzny's clinic. For physiologic reasons he prefers the term "valve lobe" to "hypertrophy of the middle lobe." Electroresection offers the best results in the presence of valve lobes. It was employed also in hypertrophy of the lateral lobes because isolated valve lobes were seen in only 11 of the 100 cases. Hypertrophy of the lateral lobes alone, or in combination with valve lobes, existed in 79 cases, carcinoma of the prostate in 8 and sclerosis of the sphincter in 2. One of the most serious complications in electroresection is hemorrhage. It was severe in 9 of the cases. Other complications were epididymitis in 7, injury of the urethra in 1, chills in 3 and high temperatures in 6. The mortality rate was 5 per cent. Death resulted in 1 case each from sepsis, coronary sclerosis and tabes, and in 2 cases from embolism. The aftertreatment required on the average twenty-one days. At the time of discharge, 45 of the patients were free from residual urine, 44 had less than 50 cc., the remaining up to 100 cc. or more, and 2 were not improved. Of the 41 patients who were followed up from one to four years, 21 had remained free from residual urine, 12 had from 10 to 50 cc. of residual urine, 4 had from 50 to 100 cc. and the remainder had from 100 to 250 cc.; 1 had to continue the use of a permanent catheter and another had a return of retention. At the Konjetzny clinic adenoma of the prostate is enucleated by the open operation whenever possible. Endo-urethral resection is resorted to when the radical operation is no longer possible. If a correct technic is employed the endo-urethral resection gives satisfactory results with freedom from catheters and fistulas.

## Bibliotek for Læger, Copenhagen

**132**:213-223 (Oct.) 1940

*Erythrothrombomonoblastosis. K. Kjerulf-Jensen.—p. 213.

**Erythrothrombomonoblastosis.**—Kjerulf-Jensen states that while his 2 patients, women aged 60 and 65 with a history of eleven and six years' duration respectively, clearly were affected differently, the following symptoms were common to the 2: (1) initial splenomegaly (extirpation of the spleen done in both), (2) changes in the blood picture (consisting of constant thrombocytemia, constant erythroblastemia and hypochromatic anemia, atypical or immature monocytes in peripheral blood, increased bone marrow activity seen in sternal punctate), (3) considerable increase in metabolism with sweating, tachycardia and palpitation, (4) bone atrophy (in the first case of Gaucher type). After splenectomy the second case took on a more leukemic character with more affected general condition. There was periodic marked hemorrhagic diathesis, with marked enlargement of the liver, moderate enlargement of the lymph nodes of the neck and universal osteoporosis. Since splenectomy, the first case has progressed slowly for seven years, the second more violently and rapidly for three years. The diagnosis is not certain in either case, and only knowledge of the future course and eventual biopsy and possible necropsy will definitely clarify the picture. Temporarily the cases are classified as chronic erythrothrombocytomonoblastosis, a sweeping protracted leukemia-like disorder of the hemopoietic system in which splenectomy is not assumed to have any decisive effect.

## Ugeskrift for Læger, Copenhagen

**102**:991-1018 (Sept. 26) 1940

*Diagnostic Value of Sternal Puncture: Review in Connection with Personal Investigations. H. Gormsen.—p. 991.
Sanatorium Treatment of Diabetes Mellitus. Agnete Bræstrup.—p. 999.
Some Clinical Vitamin $B_1$ Analyses by Aid of Mold Method. H. O. Bang.—p. 1000.
Fissure Formation in Articular Processes of Lumbar Vertebrae. V. Simonsen.—p. 1002.
Case of Fatal Carbon Monoxide Intoxication Due to Use of Charcoal Stove. H. Reistrup.—p. 1003.

**Diagnostic Value of Sternal Puncture.**—Gormsen emphasizes the decisive part played by sternal puncture in the diagnosis of less typical cases of pernicious anemia and of cases of aleukemic leukosis, myelomatosis, lipoidosis, tumor metastases to the bone and Boeck's sarcoid. Bacteriologic examination of the sternal punctate can also be of value, for example, in septicemia and typhoid. He reports on differential counts made in the bone marrow from thirty normal adults. Tumor cell complexes were demonstrated in the sternal punctate in 8 of 131 cases of malignant tumors (twenty-one sarcomas, one hundred and ten carcinomas). Metastases in the bone marrow were not established in any of the cases of sarcoma. Tumor cells were established in 7 of the 39 cases of cancer of the breast. In 1 case out of 5 with cancer of the prostate metastases were found in the bone marrow, and in 1 out of 5 cases of Boeck's sarcoid the characteristic granuloma was demonstrated in sections of the sternal punctate.

# Book Notices

**An Introduction to Gastro-Enterology.** By Walter C. Alvarez, Professor of Medicine, University of Minnesota, Minneapolis. Being the third edition of The Mechanics of the Digestive Tract. Cloth. Price, $10. Pp. 778, with 186 illustrations. New York & London: Paul B. Hoeber, Inc., 1940.

From a booklet first published in the early 1920's as "The Mechanics of the Digestive Tract" has evolved this stately volume. It is probably the most human gastro-enterology that has been published, leaning largely toward the functional rather than the pathologic aspects of the subject. The book is one of the most readable of medical works, since its author has a well established literary style and a good journalistic sense. His discussion of peristalsis is readable beyond any similar analysis of that valuable function that is elsewhere available. Indeed, the opening chapter serves merely as an introduction to a full discussion of the mechanics of bowel activity, leading eventually to an understanding of peristalsis, belching, nausea and many another symptom generally accredited to the subject of disturbance of the stomach.

Especially interesting is the insistence of the author on correct use of terms so they will mean the same things to all scientists. This emphasis on somatics is another unusual feature for a medical work. There are chapters on chewing, swallowing, on movements of the stomach, hunger pains, vomiting, the gallbladder, the colon, constipation, and eventually an analysis of surgical procedures and medical methods of study.

Since titles such as "gastric secretion" and "pancreatic secretion" do not appear in the index and since the title of this edition has been changed to "An Introduction to Gastro-Enterology," the reviewer has conjectured that this "introduction" is a first volume to be followed in the course of time by a companion volume dealing with the secretory glands which pour their digestive juices into the gastrointestinal tract. It is hoped that this conjecture is correct, for no one is in a better position to supply both the student body and the alert scientifically minded clinician with an account of the secretory side of gastrointestinal activity.

The book is replete with fine photographs of important contributors, with excellent drawings, and with supplementary chapters on books and reading, an extensive bibliography and an index. Here obviously is a "must" book for the general practitioner as well as for the gastroenterologist.

**Psychiatric Clinics for Children with Special Reference to State Programs.** By Helen Leland Witmer, Ph.D., Research Associate, National Committee for Mental Hygiene. Cloth. Price, $2.50. Pp. 437. New York: Commonwealth Fund; London: Oxford University Press, 1940.

This work is based on studies of child guidance clinic services made by staff members of the National Committee for Mental Hygiene. It provides information for those interested in the extension of psychiatric clinic service to children, particularly in nonmetropolitan areas. The author discusses the theoretical and historical background of clinical child psychiatry and the evolution of psychiatric clinics for children. She particularly emphasizes the influence of the theories and activities of Adolph Meyer, "who exerted the greatest influence on the development of child psychiatry under state auspices." The more specific contributions of freudian psychology to American child psychiatry are conservatively and constructively presented.

The second general section is a survey of state financed psychiatric clinics for children. The author finds many limitations in the programs possible under state hospital auspices and concludes that "there was little evidence that state hospitals had been much influenced by child guidance theory and practices." She describes in detail the work and services of the Northern New Jersey Clinics and of the Worcester Child Guidance Clinic, two services officially under state hospital auspices and clinics conducted by psychopathic hospitals, that is hospitals set up to observe and temporarily care for incipient and transitory mental disturbances (the Boston Psychopathic Hospital and the Colorado Psychopathic Hospital). Many factors militate against rapid progress toward the goal of developing psychiatric services extensively available to the children of rural communities. Great difficulties are encountered in having the diagnostic services of the clinics reflected in appropriate treatment steps. Limitations in local professional personnel and resources are among the handicaps.

The third section of the book, on principles for future programs, is a serious attempt by the author to evaluate the experience made available by the survey and to define the objectives of the psychiatric clinics for children. Evidence is presented indicating that clinics designed to offer psychiatric assistance for mentally retarded children can be expected to be helpful in furthering the adjustment of these children.

In a chapter on modern child guidance as a means of promoting mental health, Dr. Witmer has attempted to review psychiatric principles basic to child guidance, to contrast child guidance with other forms of child psychiatry and to outline differences in goals and methods of treatment in child guidance clinics. This is a chapter worth careful reading, although it tends to be somewhat more an interpretation of the role of the psychiatric social worker than is explicitly stated as its objective. The book concludes with a chapter on the planning of the psychiatric service for small communities.

This is a unique work, which should be consulted by all who are interested in the organization and establishment of psychiatric services for children. It is strange, however, that the author, in her discussion of the background and evolution of child guidance clinics, could have failed to make a single reference to an individual whose personal influence, practical insights and amazing organizing ability accomplished at least as much for the development of child guidance in the United States as has any other individual, namely Herman M. Adler. To be sure, the services he instituted or enriched are discussed, but the failure to include an evaluation of his influence in bringing about that synthesis of the efforts of psychiatrist, psychologist and social worker reflected in the present day organization and spirit of the Child Guidance Center is a perhaps minor but noteworthy lapse.

**Atlas of Cardioroentgenology.** By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology, Temple University School of Medicine, Philadelphia. Cloth. Price, $8.50. Pp. 124, with 166 illustrations. Springfield, Illinois & Baltimore: Charles C. Thomas, 1940.

This atlas of cardioroentgenology, by the author of Clinical Roentgenology of the Cardiovascular System, consists of sixty case reports. These reports contain a brief summary of the history, physical examination, laboratory observations and necropsy. Most of the cases are illustrated with roentgenograms in two or more positions, electrocardiograms, photomicrographs of histologic sections, and photographs of the heart made by a new method which utilizes longitudinal or window sections of the hardened specimen. The faithful reproduction of many beautiful photographs of the heart is an important feature of the work.

The first ten case reports are intended to familiarize the reader with the normal roentgen appearance of the heart. The next fifty cases deal with many common and rare diseases. Some of the common diseases described are cardiac failure, pulmonary edema, hypertensive arteriosclerotic heart disease, postural circulatory deficiency, cardiac enlargement in anemia, influence of scoliosis and funnel chest on the appearance of the cardiac silhouette, evaluation of the heart size in emphysema, elongation and dilatation of the aorta due to syphilis, aortic aneurysm, myocardial infarction, and rheumatic heart disease with mitral stenosis and other valvular lesions. Among the less common conditions described are cardiac aneurysm, metastatic cardiac tumor, intracardiac calcification associated with hyperparathyroidism, calcareous pericardial disease with cardiac compression and pneumomediastinum. Among the cases of congenital cardiac malformations are interatrial septum defect, aneurysmal dilatation of the pulmonary artery, congenital pulmonary stenosis, right sided aortic arch, and transposition of the great vessels.

Case 40, for example, contains two roentgenograms, two large photographs of the anterior and posterior aspects of the whole heart and photographs of eight sections of the heart. Case 49 is illustrated with four roentgenograms, one electrocardiogram, three large photographs of the heart and one photomicrograph.

A type page of 45 by 63 picas (about 7½ by 10½ inches) permits the use of large figures which show all essential details. The book contains a detailed table of contents but no index.

This authoritative work is a fine example of the printer's art and should be useful to roentgenologists, cardiologists and all others who are interested in diseases of the heart.

**Clinical Pathology and Treatment of the Dental Pulp and Periodontal Tissues.** By Edgar D. Coolidge, B.S., M.S., D.D.S., Professor of Therapeutics, Preventive Dentistry and Oral Hygiene, Chicago College of Dental Surgery, School of Dentistry, Loyola University, Chicago. Cloth. Price, $6.50. Pp. 461, with 289 illustrations. Philadelphia: Lea & Febiger, 1939.

This is an excellent addition to the text and reference literature on the subject. The preface says "This book is the outgrowth of many years of teaching and clinical experience in the treatment of the pulp and periodontal tissues. It represents the author's study, research, observation and deductions over a period of more than twenty-five years." Among the topics treated in the twenty chapters are dental pain and its diagnosis, treatment of the dental pulp in which vitality should be preserved, treatment of vital pulps that should be removed, removal of the pulp and preparation of root canals for filling, anatomy of root canals with relation to pulp removal and root canal fillings, principles and technic of filling root canals, healing and repair after pulp removal and root canal filling, treatment of infected pulps and pulpless teeth, treatment of teeth with inflammatory disturbances of the apical periodontal tissues, gingivitis associated with systemic disturbances, functional response to excessive or abnormal occlusal stress, treatment of functional and traumatic injuries in the periodontal tissues and treatment of suppurating periodontal pockets. The author attempts to relate treatment to tissue reaction and the biologic principles involved. He discusses all the accepted methods and gives the reasoning on which the advocates of these methods base their program. The attention of the medical profession is especially called to chapters IX, X and XI. A careful study of these chapters would help to clear up much of the misunderstanding that has existed with reference to the pulpless tooth. The work is profusely illustrated with a large number of photomicrographs. As a specimen of book making it is fully up to the high standards of the publishers. It will be a valuable student textbook and of unusual interest to the clinician.

**Die Methoden der Fermentforschung.** Unter Mitarbeit von Fachgenossen. Herausgegeben von Prof. Dr. Eugen Bamann und Prof. Dr. Karl Myrbäck. Lieferung I. Boards. Price, 18 marks. Pp. 172, with 2 illustrations. Leipzig: Georg Thieme, 1940.

This is the first published section of a projected reference work on enzyme research. When completed it will be about 3,500 pages long and will cover the chemistry and preparation of substrates, the methods of following enzyme activity, the detailed description of enzymes and the applications, industrial and clinical, of enzyme chemistry. The present section deals with the preparation, properties and mode of use of the following classes of substrates: the glycerides, acetylcholine, the tannins, chlorophyll, phosphoric esters, phosphatides, sulfuric acid esters, hexoses and glycosides. The treatment is detailed, thorough and systematic. If the work as a whole keeps to the standard set by the present section, the handbook will be indispensable to workers in the field of enzyme chemistry. The American contributors will include R. S. Anderson, M. L. Anson, E. N. Harvey, Moses Kunitz, J. H. Northrop and J. B. Sumner.

**The Histamine and Insulin Treatment of Schizophrenia and Other Mental Diseases.** By Horace Hill, M.R.C.P., Medical Superintendent, Laverstock House Mental Home, Salisbury. Cloth. Price, $1.75. Pp. 133. Baltimore: William Wood & Company, 1940.

The author states that histamine is present not only in insulin shock but in every variety of shock and, further, that evidence goes to show that in the cases of induced fits (i. e. convulsion therapy) the thing of essential importance is not the actual fit but the histamine formed. These statements, mainly the first parts of them, one can hardly argue away. The originators of the insulin and convulsion treatments themselves never believed or stated that the curative agent of the so-called shock therapies is the shock itself. On the contrary, they always emphasized that the biochemical changes connected with the shock are of primary importance. What these unknown factors are, the mutual and forced work of innumerable researches here and abroad have not determined for the time being. Unfortunately the flat assumptions of the author cannot replace meticulous research work. Not regarding, however, the weakness of its theoretical bases, the method, being presumably without dangers, is worthy of a trial. The treatment comprises a series of three or four treatments each consisting of from fifteen to twenty injections of 5 to 10 units of insulin combined with 0.2 to 2.0 mg. of histamine. The injections may be given daily or, better, every second day. The reactions of the patients are slight as compared to the shock treatments; however, the treatment is contraindicated in cases of asthma, increased blood pressure, heart and liver disease, thickened and stiff arteries and pregnancy. The author claims that his method has more effect in chronic cases than other methods. In addition the book contains thirty case histories which are sometimes convincing, though the classification of the results as "well," "improved" and "indefinite" sounds itself rather indefinite.

**Veterinary Bacteriology.** By I. A. Merchant, D.V.M., Ph.D., C.P.H., Associate Professor of Veterinary Bacteriology and Hygiene, Iowa State College, Ames. Cloth. Price, $7. Pp. 628, with 135 illustrations. Ames: Iowa State College Press, 1940.

The author has arranged a curriculum for undergraduate students of veterinary medicine covering the more common pathogenic micro-organisms affecting domestic animals. On the valid and customary ground that bacteriology has a broader definition than the word indicates, molds, yeasts, filtrable viruses and bacteriophage are included. Protozoa, however, are left for the parasitologist. The opening chapter is a brief but quite accurate account of the historical events which led to the present conception of micropathology. Infection, immunity, anaphylaxis and serologic tests are outlined. The technics and methods related are those commonly employed in the teaching of elementary bacteriology. The terminology, classification of bacteria and the descriptive material conform to modern usage. The more important species of Salmonella affecting man and animals are singled out for particular attention. The species of this genus are well chosen and well described as to their history, their hygienic significance and the laboratory methods now employed in classifying them. The chapter on filtrable viruses lacks some of the newer knowledge of the nature of viruses and virus infections but is nevertheless a reminder that veterinarians are entitled to a great deal of credit for having conquered by vaccination such grave virus infections as hog cholera, canine distemper, avian variola, rinderpest, and equine encephalomyelitis. The fault of this book is the brevity of the contents, owing to the usual attempt to cover everything related to medical bacteriology in a too small volume.

**Surgical Nursing.** By E. L. Eliason, A.B., M.D., Sc.D., Surgeon, University of Pennsylvania, Philadelphia General and Presbyterian Hospitals, Philadelphia, L. Kraeer Ferguson, A.B., M.D., F.A.C.S., Assistant Professor, University of Pennsylvania Medical School, Philadelphia, and Evelyn M. Farrand, R.N., B.S., Instructor in Nursing Arts and Surgical Nursing, University of Pennsylvania Training School for Nurses. Sixth edition. Cloth. Price, $3. Pp. 673, with 245 illustrations. Philadelphia, Montreal & London: J. B. Lippincott Company, 1940.

There is always a good reason why some books become popular and require a number of editions at frequent intervals. In this case the reason is evident. This book on surgical nursing is everything a textbook on this subject should be. In clear and simple language it covers the entire field of surgery briefly but adequately enough to give the student nurse an ample insight into the subject. In addition there are clear, concise descriptions not only of what to do and how to carry out each procedure but also why it should be carried out in a certain way. For this reason there are sections on anatomy, physiology and microbiology as applied to the surgical principles involved in nursing care. The book is accurate and abreast of the times. It includes discussions of the Wangensteen suction apparatus, the use of the Miller-Abbott tube, chemotherapy and the newer drugs and anesthetics. The large number of well prepared photographs, diagrams and drawings illustrating individual points of technic vividly enhance the value of the text. Altogether this book is what it was intended to be, a textbook on surgical nursing, and it is an excellent one.

# Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

## CEREBRAL VASCULAR LESIONS AFTER CARBON MONOXIDE POISONING

*To the Editor:*—**A white man aged 37, a laborer, was treated on Nov. 8, 1940 in our hospital by another physician for two days for carbon monoxide poisoning, apparently making a good recovery. On November 27, while working as a laborer, he had a sudden severe pain in his head and was brought to the hospital for observation. Pain in the head was accompanied by vomiting. Blood cell counts were as follows: November 27, erythrocytes 4,600,000, leukocytes 6,250. On Dec. 7, 1940 he was normal apparently in every respect. Blood cell counts were normal. His discharge was considered. About 3 a. m. on December 8 he had more cerebral pain with vomiting and lapsed into unconsciousness. The pulse was about 48, respiratory rate 10, blood pressure 94 systolic and 60 diastolic. Spinal puncture revealed bloody spinal fluid under considerable pressure. In spite of all treatment, including oxygen, he died at 4:45 p. m. There was no history of injury to the head, and the question has arisen as to whether carbon monoxide poisoning, which occurred about a month ago, could have caused cerebral hemorrhage and death.**

**W. H. Paige, M.D., Brownwood, Texas.**

ANSWER.—This question cannot be satisfactorily answered in view of the fact that no real data are given covering the degree of asphyxia experienced by the patient when poisoned on or about November 8. Since he was hospitalized over several days presumably his asphyxia was great. The following material from Drinker's book (Drinker, C. K.: Carbon Monoxide Asphyxia, New York, Oxford University Press, 1938) on carbon monoxide poisoning seems pertinent:

"Semerak and Bacon (1930) have written an excellent summary of the literature on vascular lesions not only in the brain but in the body generally. There is no doubt that fatty, hyaline and other retrogressive changes of vessel walls, particularly of the small arterioles, may follow gas poisoning of severe grade and that the actual duration of asphyxia necessary to produce such changes may be as short as twenty minutes. A very different question arises in connection with the possible causation or intensification of arteriosclerosis as a result of chronic or of relatively mild single exposures. In my opinion there are no reliable pathologic data to support such contentions, though the issue has been raised medicolegally in the past and will undoubtedly be raised again.

"The effects of carbon monoxide on blood vessels are undoubtedly more severe in old people with a certain degree of antecedent arteriosclerosis than they are in young persons with normal vessels. As a result, an old person may emerge from a severe gassing with a hemoplegia, or may develop such a condition suddenly a week to three weeks after the accident."

## WATER SOLUBLE BISMUTH FOR TUBERCULOSIS

*To the Editor:*—**I have received reports of the treatment of pulmonary tuberculosis by the intravenous injection of water soluble bismuth. Will you give me the status and your opinion as to this form of therapy.**

**J. D. Riley, M.D., State Sanatorium, Ark.**

ANSWER.—Bismuth compounds have been used in medicine since about 1785. The insoluble salts of bismuth have been employed extensively on inflamed surfaces, as they have a mechanical or protective action. When applied to wounds or to inflamed mucous surfaces they dry the secretions and form a protective covering. A small amount of bismuth goes into solution and has a mild antiseptic action. The insoluble compounds are opaque to the roentgen rays and therefore have been used in outlining the shape of the stomach and intestine. The soluble bismuth salts do not possess the soothing qualities of those which are insoluble and therefore it is irrational to employ them on inflamed surfaces, including mucous membranes.

During this century it has been found that when aqueous or oil solutions of bismuth are administered intramuscularly in small doses they have a beneficial effect in syphilis by checking and suppressing the infection. The best effects are obtained when repeated doses are injected into muscle periodically, from which it is slowly absorbed and distributed to various parts of the body. Indeed, intramuscular administration is the only safe method of introducing enough bismuth to be effective. Even when injected in this manner, watery solutions often result in considerable pain, swelling and induration, which may persist for several days. As bismuth is absorbed, it is distributed throughout the body but in varying concentrations in different parts. The total accumulated bismuth has been found in animal tissues to be approximately 40 per cent in the kidneys, 19 per cent in the bones, 13 per cent in the liver, 8 to 10 per cent in the muscles, 7 to 8 per cent in the skin, 2.5 per cent in the lungs and 7 per cent in all the other tissues. Doses of bismuth as large as those introduced intramuscularly when injected intravenously are dangerous and may be fatal because of the tendency of bismuth to form insoluble compounds with resulting flocculation shock. There is an immediate fall of blood pressure. If this does not result fatally there is a fairly prompt recovery of normal pressure. This action has been determined to be due to disturbed conduction and heart block.

Bismuth in the alimentary canal precipitates hydrogen sulfide and when introduced into the blood stream because of the hydrogen sulfide, which is always present in the large intestine, this precipitation may occur in the vessels of the large bowel with resulting capillary embolism and ulceration, as indicated by pain, diarrhea, vomiting and other symptoms of colitis. Thus, the effects of bismuth on the animal and human body are reasonably well known.

Rénon (*Bull. et mém. Soc. méd. d. hôp. de Paris* **44**:602, 1920) states that more than twenty salts of rare earths and other elements inhibit the growth of tubercle bacilli in vitro. This group includes bismuth, gold and silver but, unfortunately, much work done since this report has shown that not one of these substances, or any other, has been found to cure tuberculosis either in man or in experimental animals. Such preparations do not reach the tubercle bacilli in sufficient concentration to have enough effect to justify their administration nor do they cause fibrosis to a sufficient degree to heal tuberculous lesions. Therefore there is no evidence that the intravenous administration of water soluble bismuth in dosage of any size has a significant effect on tubercle bacilli or the lesions they produce in the human body. Indeed, bismuth introduced directly into the blood stream is actually capable of doing harm.

## TRICHOMONAS INFECTION OF BLADDER

*To the Editor:*—**A white woman aged 47 had a Trichomonas vaginalis infection of the vagina and bladder. I have been treating the vaginal infection with floraquin tablets, vinegar douches and silver picrate suppositories. Smears from the vagina are now negative and there do not seem to be any signs of vaginal irritation. I have been treating the infection of the bladder by instillations of 0.5 per cent silver picrate solution into the bladder daily and the use of sulfanilamide, sulfathiazole and mandelic acid by mouth. Instillation of silver picrate solution will apparently clear up the infection of the bladder as long as I continue to use it every day. However, on discontinuing treatment, within four or five days' time I find in the catheterized specimen of urine from eight to ten Trichomonas organisms per high power field. I would appreciate any suggestions you may have with regard to treatment.**

**M.D., Mississippi.**

ANSWER.—The first case of invasion of the bladder by Trichomonas vaginalis was reported by Marchand (*Zentralbl. f. Gynäk.* **15**:709, 1894). Following this a number of single case reports appeared, giving the impression that the occurrence is rare. However, Heckel (*J. Urol.* **35**:520 [May] 1936) reported a series of 43 cases, and Nitschke (*West. J. Surg.* **45**:278 [May] 1937) reported 13 cases. The latter author mentions that Zenner found Trichomonas vaginalis in the urine of 6 women in a series of 132 cases of Trichomonas vaginitis infection. In this series, 36 women complained of urinary symptoms. Some authors maintain that there is a typical change in the bladder mucosa which is characteristic of a Trichomonas infection. Allen (*Am. J. Surg.* **33**:523 [Sept.] 1936) says "The mucous membrane change is usually limited to the urethra or the trigon of the bladder. A fluffy, edematous, almost leukoplakic looking area surrounded by or containing within its borders petechial-like spots similar to those found in the vaginal mucous membrane help identify the lesion at once." Nitschke denies that there is a pathognomonic cystoscopic picture.

In at least one case (Visher, J. W.: Vesical Infection with Trichomonas Vaginalis, THE JOURNAL, June 22, 1929, p. 2098) not only was the bladder involved but also probably the kidney. The most likely avenue of infection of the urinary tract is the urethra. In some cases the bladder infection is so severe that relief is sought only because of bladder disturbances and not because of a vaginal discharge. In many cases of bladder involvement in cases of Trichomonas vaginalis infection the organism cannot be found in the urine.

Various forms of therapy have been recommended. In Visher's case the condition rapidly improved after vesical and pelvic lavage with mercurochrome. Bladder irrigations with boric acid solution were followed by instillation of ½ ounce (15 cc.) of mercurochrome solution every day for a few days, then at three

to seven day intervals for a few weeks. The cervix and vagina were also treated with 6 per cent mercurochrome solution.

There may be an error in believing that Trichomonas is present in the bladder in the case under consideration. As Karnaky (*Urol. & Cutan. Rev.* **40**:823 [Nov.] 1936) pointed out, Bodo urinaria (caudatus), which is often mistaken for Trichomonas, is often found in the urine with and without Trichomonas vaginalis. The shape of Bodo caudatus resembles that of a cigar and it does not change its shape as much as Trichomonas vaginalis. The latter is somewhat larger and less active than Bodo urinaria.

## DURAL METAL PRODUCT AND CUTANEOUS ULCERATION

***To the Editor:***—**Recently I have been treating a young man who has been taking an apprentice course in sheet metal work in an airplane factory. He tells me the name of the metal with which he works is "Dural." For several weeks he has had two chronic ulcerative lesions, one on the dorsal surface of each hand. The larger of the two is about the size of a dime (18 mm.). He came under my care at first because of an associated lymphangitis that seemed to travel up the arm to the axilla in about two hours. This subsided almost as rapidly when the focus on the hand was treated but has flared up in a similar manner once since. Both times when the lymphangitis occurred he did not complain of any systemic ill feeling but witnessed considerable throbbing pain of the hand and arm. There was no elevation of temperature and a blood count taken showed nothing unusual except a slight rise of the lymphocyte count to 49 per cent. I was unable to determine whether the dust that he says forms when the metal is being worked was mechanically rubbed into the tissue through the intact skin or whether it entered through already abraded areas. I have been unable also to find out just what alloy Dural is but the patient tells me that he knows it contains aluminum. Is this a common reaction to this metal or is it a special sensitivity that he has to it? I should also like to know what advice I should give him about continuing with the work under either circumstance.**

**M.D., New York.**

ANSWER.—Dural, or 17 S. T., a metal product of the Aluminum Company of America, consists approximately of copper 4 per cent, magnesium 0.5 per cent, manganese 0.5 per cent, iron a trace, silicon a trace and aluminum the remainder. Sheets of this metal are customarily marketed without a coating of antiscoring oil, which oil has been the source of much dermatitis among some sheet metal workers. No one of the metals mentioned as constituents of Dural are common sources of dermatitis among metal workers nor does the cutaneous lesion described especially suggest a metal dermatitis with the possible exception of chrome ulceration. Mechanical abrading by metal particles may be the source of the damage to the skin but, if true, this might be expected from any metal. There is a possibility that an idiosyncrasy to some metal in "Dural" may be present, but many thousands of sheet metal workers manipulate this metal without specific injury to the skin. The average sheet metal worker comes into contact with other substances better known to cause a dermatitis. The number includes harsh soaps, solvents used for cleaning the skin such as naphtha, oils about machines, and degreasing agents. Inquiry as to personal hygienic practices is more promising to the disclosure of the cause of this ulceration than may be expected from any chemical or sensitizing action from the metal components. The new worker (young apprentice) may be far more responsive than experienced and inured workers to minor irritants present about metal shops. There is no known reason why this apprentice should be advised to discontinue his employment—at least until further events reveal some especial and uncontrollable sensitivity to this metal or ancillary work materials.

## QUINIDINE AND DIGITALIS

***To the Editor:***—**During the past eight years I have had two unfortunate endings after the administration of quinidine in auricular fibrillation. Both of the patients had been previously digitalized. At a recent medical meeting I heard the speaker state that in a case of his in which he had prescribed digitalis and had not quite controlled the irregularity he was induced by another internist to try quinidine. He did, with the almost immediate death of the patient. Do you know of any synergistic effect or incompatibility either chemically or physiologically of quinidine in a previously digitalized heart as may exist between digitalis and calcium?**

**M.D., Nebraska.**

ANSWER.—There is no evidence in the literature or in the pharmacologic properties to indicate a chemical incompatibility of digitalis and quinidine. Digitalis and quinidine have been frequently used together in the attempt to convert an auricular fibrillation to a normal sinus rhythm. Good results, and an occasional fatal outcome, have been reported by many observers. The fatal results have been attributed to cerebral embolus, cardiac standstill or ventricular fibrillation. However, deaths are reported when quinidine is used alone in the treatment of cardiac arrhythmia, so the concurrent use of digitalis must not always be blamed. Digitalis causes a depression of auriculoventricular conduction and when used excessively can cause bizarre ectopic rhythms and eventually ventricular fibrillation; the further addition of a drug which also causes depression of conduction tissue, such as quinidine, may thus be enough of a factor at times in causing sudden death. Gold and his co-workers have shown that this is true in dogs. Quinidine must always be given a therapeutic test trial to eliminate the possibility of cinchona sensitivity. Such accidents as reported are rare, but in an effort to prevent their possible occurrence the pharmacologic actions and indications and contraindications of these drugs should be fully understood.

References:

Gold, Harry; Modell, Walter, and Price, Leo: Combined Actions of Quinidine and Digitalis on the Heart, *Arch. Int. Med.* **50**:766 (Nov.) 1932.

Kwit, N. T., and Gold, Harry: Further Experimental Observations on the Combined Effects of Digitalis and Quinidine on the Heart, *J. Pharmacol. & Exper. Therap.* **50**: 180 (Feb.) 1934.

## FLUORESCENT LAMPS FOR READING

***To the Editor:***—**Is a fluorescent lamp advisable for use as a bed lamp (at close range)? For a patient aged 63, confined to bed in a room where artificial light is required all day because of a hooded porch and close trees, what power globe should be used? The lamps are sold in Seattle in "15 inch tubes," I understand, but what wattage that is I do not know. I am using a hundred watt electric globe with a reflector, which is unsatisfactory because of the glare. The eyes were originally good but suffer from constant reading under these conditions. Is the General Electric Mazda fluorescent globe the best?**

**M.D., Washington.**

ANSWER.—Fluorescent lamps are excellent for reading, provided they are properly arranged so that the light does not come from in front of the patient but from behind and from a sufficient distance above. The lamps are not powerful (which is one of their advantages, because the light is not so glaring), so that sometimes more than one of the 15 inch tubes is needed.

Probably one could have obtained satisfactory results with the ordinary incandescent globe, provided the reflector had been so placed as to throw the light up on the ceiling and on the wall behind the bed, instead of, as it probably was, with the reflector above throwing the light down on the book or work. A hundred watt incandescent bulb would probably not be enough for the indirect lighting with the reflector throwing the light on the ceiling and the wall. It would depend on how light the walls were. With a white wall and a white ceiling 100 watts would be enough but not with the darker walls and ceilings.

## PASSIVE IMMUNITY TO POLIOMYELITIS

***To the Editor:***—**1. Can a mother who has had infantile paralysis some time previously pass immunity to her child? 2. Would a child born of such a mother keep his immunity for four to six years?** **M.D., Illinois.**

ANSWER.—1. Any mother whether she has had poliomyelitis or not has virucidal antibodies which pass through the placenta to the baby, thus transferring a passive immunity which may persist five or six months. There is no evidence that a person who has had the disease would pass more antibodies than one who has never been afflicted. 2. Such a passive immunity is of a temporary character and would not last four to six years. A third question suggests itself: "Could the serum of a mother who has had infantile paralysis be used to protect passively her 4 or 6 year old children exposed to the disease?" It is not believed that the mother would have at the time more blood serum antibodies than any normal person. The best passive immune principle for therapeutic purposes is obtained from a patient a little while after he has recovered from the infection.

## ROENTGEN THERAPY FOR PROSTATIC HYPERTROPHY

***To the Editor:***—**What is the present status of roentgen therapy in cases of hypertrophied prostate?** **M.D., New York.**

ANSWER.—There is considerable difference of opinion among urologists and radiotherapists as to the effect of roentgen therapy on benign prostatic hypertrophy. The more conservative incline toward the opinion that the only effect of irradiation is a reduction in the associated congestion and edema, giving temporary relief in selected cases. It cannot be regarded as a substitute for prostatectomy or transurethral resection. In view of the great diversity of opinion among the profession as to the effect of roentgen treatment for this condition, further experience with this therapy will be necessary before its true status can be determined.